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Intrathecal administration of 4-aminopyridine in chronic spinal injured patients

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Study design: Intrathecal administration of 4-aminopyridine (4-AP) in chronic spinal cord injured (SCI) patients.
Objective: To determine the safety and effects of intrathecal administration of 4-AP in a small population of chronic SCI patients.
Setting: The post anesthesia care unit of a tertiary care hospital.
Methods: Following animal mode studies to establish dosing safety, six subjects with chronic SCI were examined. In each subject, an intrathecal catheter was placed with the tip as close to the lesion level as possible. 4-AP was infused at 5 μg/h for a period of 4–5 h. Vital signs were recorded and sensory-motor physical examinations and pain questionnaires were administered for 24 h. In two patients, samples of cerebrospinal fluid for analysis were drawn from a second intrathecal catheter.
Results: No adverse systemic side effects were noted. One patient showed transient improvement in sensory function; two showed transient increases in spasticity; three showed transient increases in cutaneomuscular reflexes and two showed an apparent small increase in volitional motor control. The concentration of 4-aminopyridine in the cerebrospinal fluid reached a peak of 163 ng/ml at 4 h in one subject and 122 ng/ml at 5 h in the other subject examined.
Conclusion: Intrathecal administration of 4-aminopyridine at a rate of 5 μg/h does not appear to cause adverse effects and may modify spinal cord function. This route of administration allows local cerebrospinal fluid concentrations equivalent to those produced by maximum tolerable systemic doses, which require 1000 times more drug substance to be delivered to the subject as a whole. Intrathecal administration offers the potential to focus therapeutic effects to the lesion site while minimizing systemic side effects.
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Introduction

A number of clinical trials in recent years have examined the effects of 4-aminopyridine (fampridine, or 4-AP) in chronic spinal cord injury (SCI) patients. This drug, a blocker of fast potassium channels in neural membranes, has been shown to improve conduction in demyelinated axons under a variety of experimental conditions, including preclinical models of SCI.[1–3] It may also act by enhancing synaptic transmission, though the ability to do this at clinically tolerable, systemic doses is not established.

The earliest clinical studies examined the safety of intravenous infusion of the drug in small numbers of subjects. These studies provided limited evidence of efficacy, showing small changes in electrodiagnostic indicators[4] and more substantial sensorimotor effects, including an unexpected relief of chronic pain and spasticity, within a double-blind, crossover designed trial.[5] Similar effects were confirmed in a third study, an open trial in six patients, which also encountered a remarkable recovery of bowel control and sexual function in one subject. Further studies of prolonged oral administration of 4-AP have reported maintained clinical benefit in some patients.[6,7] Most recently, a double-blind placebo-controlled study of a sustained-release 4-AP formulation in chronic incomplete SCI patients has demonstrated significant efficacy on a number of neurological measures.[8] Changes in

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conduction in motor pathways have also been documented electrophysiologically in man using transcranial magnetic stimulation.[9]

Together with a longer series of equivalent trials in multiple sclerosis,[10–12] these studies indicate that 4-AP may be useful in the treatment of conduction deficits in demyelinating conditions. Chronic SCI appears to be a particularly suitable target because of the relative stability of the associated anatomical and physiological deficits, at least after the first year following injury. Beneficial responses to treatment should therefore be discernible against this stable background and reasonably attributable to the invervention.

However, 4-AP does present the potential for adverse side effects, of which the most serious so far have been seizures. Such side effects at high doses are a necessary consequence of the mechanism of action. The narrow therapeutic index of 4-AP may restrict the ability to obtain maximal benefit from oral or intravenous administration of the drug. The present study examined the possibility that intrathecal delivery through a catheter placed at the site of injury might allow higher levels of drug concentration to be achieved safely, without adverse effects on the rest of the nervous system. This followed an initial double-blind, crossover study that examined the effects of intravenous 4-AP compared with vehicle placebo in a group of 12 patients.[13] Both studies were carried out with the approval of the Institutional Review Board of Baylor College of Medicine.

Methods

Six patients were selected from a group of 12 enrolled in a previous intravenous 4-AP study (Table 1).[13] These patients had been recruited from a population of chronic spinal cord injury patients referred to The Institute for Rehabilitation and Research for their rehabilitation care including the management of problems related to pain and/or spasticity.

The patient was prepared for intra-operative placement of an intrathecal catheter (Medtronic AlgoLine^{TM}), during which monitored anesthesia care (MAC) anesthesia was administered. Under fluoroscopic imaging, an intrathecal catheter was carefully placed to the lesion level. When the catheter would not advance beyond the lumbar region it was kept at that level. In two cases an additional catheter was placed to the lesion level for sampling of cerebrospinal fluid (CSF). The patient was then transferred to the post-anesthesia care unit for recovery and examination.

After a period of 30 min to 1 h, a baseline measurement of the patient's neurologic and neurophysiologic profile was made by: (1) a standard clinical neurological examination including American Spinal Injury Association (ASIA) motor and sensory scores;[14] (2) a spasticity assessment using the Ashworth scale;[15] and (3) a modified McGill pain questionnaire.[16] A solution of 10 μg/ml of 4-AP was formulated using 0.5 mg of 4-AP, 0.45 g of NaCl, 2 ml of HCl (to pH 7.3) and H_2O to make a total volume of 50 ml. An exception was made for the first patient, where the 4-AP concentration was 5 μg/ml. The 4-AP was typically delivered at a dosage of 5 μg/h (0.5 ml/h) for 4–5 h through the intrathecal catheter attached to an infusion pump (MiniMed^{TM}), with the exception of the first two patients examined where the dosage was reduced. Infusion was terminated if adverse side effects were noted.

The patient's vital signs were monitored at 30-min intervals throughout the procedure. The neurological examination, spasticity assessment and pain questionnaire were performed at 1-h intervals during the infusion and at 1 and 24 h post-infusion. CSF samples were obtained at 1-h intervals during infusion and at 15 or 30-min intervals post-infusion. 0.5 ml were first drawn through the catheter for discard and 0.5 ml was saved and frozen within 30 min at less than -20°C for storage and shipment to the analysis laboratory. 4-AP concentrations in the CSF samples were measured using a previously validated high-pressure liquid chromatography (HPLC) technique, by PHARMout Laboratories (Sunnyvale, CA, USA). The method has a quantification limit of 2.00 ng/ml for 4-aminopyridine, using 0.5 ml of CSF for analysis. Accuracy and precision of analyses were monitored by concurrent analysis of samples of normal CSF (from subjects outside the study) spiked with known quantities of 4-AP.

Table 1 Patient description and injury characteristics

	Subject			*Injury*			
ID	*Gender*	*Age*	*Weight* (kg)	*Level*	*AIS*	*Years post-injury*	*Etiology*
2	M	30	93.6	T-10	A	3	GSW
24[b]	M	66	91.8	T-02	A	6	FALL
4	M	61	71.3	T-09	B[a]	27	FALL
23[b]	M	53	84.4	T-04	B[a]	6	FALL
12	M	47	125.0	L-02	C	2	MVA
18	F	30	59.9	T-04	D	10	MVA

[a]Borderline neurologocally complete, with minimal sacral sparing of sensation only. [b]Subjects in whom CSF samples were collected for 4-AP analysis

Results

Subject population

The demographic characteristics of the patient group are listed in Table 1, ordered by the severity of neurological deficit. Five males and one female ranged in age from 30 to 66. All had sustained thoraco-lumbar injuries, two were neurologically complete, two were borderline complete, but characterized as sensory incomplete by the ASIA standard,[17] one was motor incomplete (at L2) with an ASIA impairment of C, and one (the female) was motor incomplete with a classification of D. Subjects varied between 2 and 27 years post-injury.

Intrathecal catheterization

Placement of the intrathecal catheter to the level of injury was successful in five of the six patients. In case 4, the catheter could not be inserted beyond the L-2 vertebral level and could not be passed to the T9 level of injury. Figure 1 shows a radiograph of catheter placement in one subject (number 2) with a clear residual dislocation of the vertebrae, allowing the injury site to be identified directly. The path of the catheter as it passed rostrally in the subdural space was characteristically unpredictable. In this case it ran on the ventral aspect of the spinal cord, but in other cases remained in the dorsal midline. In two cases (patient numbers 23 and 24) a second catheter was placed independently, with the tip approximately 1 cm from the tip of the delivery catheter.

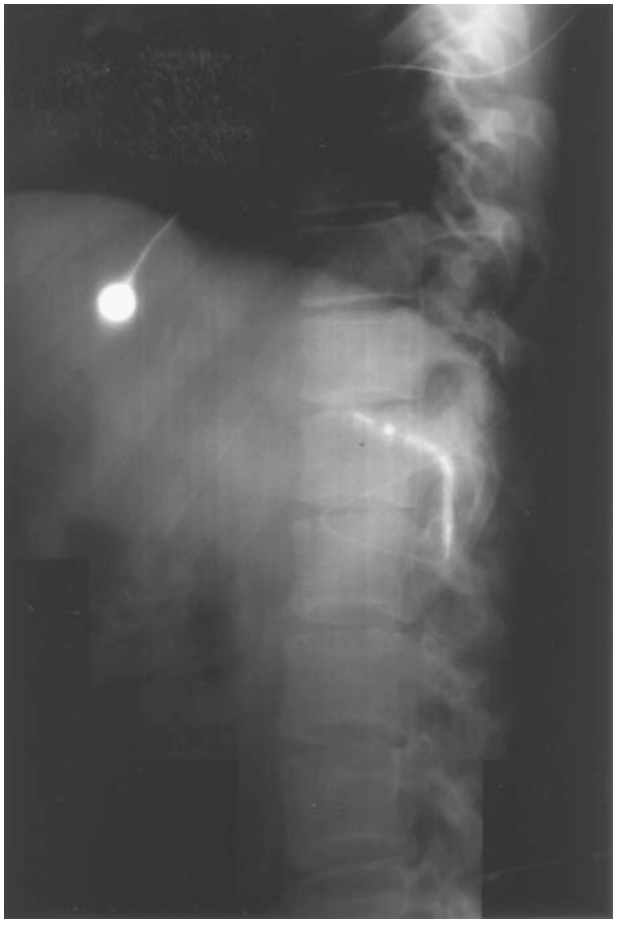

Figure 1 Radiograph of catheter placement in one subject (number 2). Note the clear residual dislocation of the vertebrae

All six subjects received 4-AP by intrathecal catheter. Initially, infusion was begun at lower rates and then increased to the maximum rate of 5 μg/h established from the previous animal toxicology study. The first subject (patient 2) received a gradual escalation: 2 μg/h (0.4 ml of 5 μg/ml) for 1 h, 3 μg/ml (0.6 ml of 5 μg/ml for 1 h, 4 μg/ml of 10 μg/ml) for 1 h, and 5 μg/h (0.5 ml of 10 μg/ml) for the last hour. Subject 12 received an hourly dose escalation: 2, 3, 4 and 5 μg/h (0.2–0.5 ml/h of 10 μg/ml) over the course of 4 h. Subject 18 received 2 μg/h for the first hour, then 5 μg/h for another 4 h. The other three subjects received the drug at a rate of 5 μg/h (0.5 ml/h) for 4 h (patient 4) or 5 h (the two subjects, 23 and 24, in which CSF was sampled).

Adverse events

There were no serious adverse events during the study. No clinically significant changes were noted in vital signs.

Subject 2 complained of headaches for a period of 2 days following the procedure. Subject 12, with lumbar injury and infusion over the cauda equina, experienced a burning sensation localized to the right anterior thigh, and focal fasciculations appeared in the right quadriceps muscle. Both conditions resolved rapidly following the scheduled termination of infusion. Subject 18 complained of pain in the groin area, beginning in the 4th hour of infusion. The infusion was terminated as a result of this and the condition resolved in less than 1 h when the catheter was removed. Subject 23 reported severe spasms in the night of the day following the procedure.

4-aminopyridine levels in CSF

For the two subjects in which it was possible to meaure CSF levels of the drug, the concentration rose rapidly for 1–2 h from the start of infusion, and only slowly thereafter (Figure 2). The maximal levels achieved in the two subjects were 122 and 163 ng/ml. At the end of infusion, the levels dropped rapidly, with a half-time less than 1 h. The difference in maximal concentration between the two subjects was accompanied by a difference in time course that may have indicated a greater separation of catheter tips in subject 23 compared to subject 24.

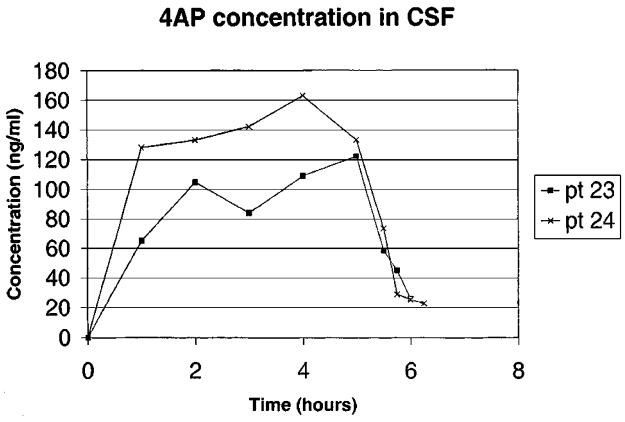

Figure 2 Concentration of 4-aminopyridine in the cerebrospinal fluid taken from two subjects before, during, and after intrathecal infusion of 4-aminopyridine at a rate of 5 μg/h

Neurological changes
None of the subjects showed pronounced neurological changes during the study. Subjects with the more severe injuries (ASIA classification A and B) showed few changes of any kind other than a tendency for increased reflex muscle response to cutaneous stimulation in some individuals. The two less severely injured subjects (ASIA C and D) appeared to experience more complex responses. Changes in responses of the patients were sufficiently different from each other to require case-by-case description:

Subject 2 At 1 h following the beginning of drug infusion, sensory testing (pinprick) began to evoke muscle twitches that were not seen at the baseline examination. This evoked activity increased during the infusion period, and began to decline by 1 h after the end of infusion. The muscle activity began distally with the great toe extensors and appeared to move proximally up to the hamstrings and quadriceps as the activity increased during the 4-h infusion.

Subject 24 There were no notable neurological changes in responses of this subject.

Subject 4 No muscle spasms or twitches were noted in the subject during the baseline examination. During the 4-h and 5-h examinations, short stimuli at the sacral level evoked a rectal sphincter muscle twitch on both the right and left sides.

Subject 23 There were no notable neurological changes in responses of this subject.

Subject 12 This subject appeared to experience some changes during the 24-h trial. Some minor fasciculations appeared during the 3-h examination in the right anterior thigh. The subject experienced some strength gain in the ankle plantarflexion movement. At the 2-h examination, the right ankle improved slightly, but the left one noticeably improved in that it went from a palpable contraction (ASIA grade 1) only to full range of movement with gravity eliminated (ASIA grade 2).

During the 3-h examination, a severe burning pain developed in the right anterior thigh. Approximately 9 min later, focal fasciculations began in the right quadriceps muscle and continued throughout the remainder of the examination.

Subject 18 No spontaneous muscle fasciculations or spasms were detected during sensory testing until the 3-h examination. At 3 h, the subject began to experience muscle twitches in response to the sharp stimuli in the lower extremities. These muscle twitches continued during the 4 and 5-h examinations, but at a significantly lower incidence. None were noted during the 24-h examination.

This subject reported improvements in bowel function (control), lower extremity motor strength, reduced spasticity, and increased endurance at 1 month after the study. These improvements were maintained at a 6-month follow-up interview.

The neurological examiner at the 24-h examination also reported improvement in right lower extremity motor function, relative to baseline. However, these improvements did not reverse following the study and were still present at 6 months thereafter. The subject felt that her motor improvements were attributable to the treatment. Confirmation of this from the records of earlier ASIA neurological examinations was difficult to obtain, because measurement of motor function in the right limb was obscured by evoked muscle spasms in a number of earlier examinations. However, on the day of the study itself, all the muscle groups in the right leg were scored at 0 (total paralysis) although there is support for a reduction in spasticity of hip flexors, knee extensors and ankle plantiflexors, which may have revealed more underlying motor control. Also, a subjecting recovery of hip extensor function could not be confirmed, as this muscle group is not part of the standard neurological examination.

Discussion

The results of the study are most important in demonstrating that relatively high local concentrations of 4-aminopyridine can be achieved safely with intrathecal delivery of very low total doses. Peak concentrations of 121 and 162 ng/ml seen in two of the subjects were equivalent to peak plasma levels seen in previous studies of maximal tolerable systemic doses.[5] On the other hand, data from the intravenous portion of this study[13] indicate that the concentration expected in the CSF is only about 50% of that seen in the plasma, therefore the local concentrations achieved seem likely to be higher than those that have been produced with systemic administration.

These local concentrations appeared to be sufficient to produce localized increases in reflex responses to

cutaneous stimulation, and even sufficient to focal muscle fasciculation, but did not clearly lead to clinically useful improvements in function. This may indicate that the delivery from a single intrathecal catheter may be too localized to be broadly effective. It has not been determined whether beneficial effects of the drug observed experimentally are obtained at the site of injury or by a much less focused increase in the excitability of the nervous system, particularly at the synaptic level.

This interpretation must be qualified by the fact that, in this study, the drug was delivered for a short period of time (4–5 h) during which the subjects were not free to move around or experience any potential effects on their normal function or quality of life. The interpretation must also be tempered by the fact that the patients in this study were drawn from a larger group of 12 who participated in a study of intravenous delivery of the drug, which itself failed to demonstrate any significant clinical benefit, in contrast to some previous studies. Therefore, this particular selection of subjects may not have been susceptible to improvement based on this approach. In addition, it should be noted that four of the six subjects in this study were essentially neurologically complete injuries, and none of the few subjects with complete spinal cord injury in previous studies of 4-aminopyridine has evidenced signs of beneficial effects of the drug on neurological function.

With regard to the dosage of intrathecally infused 4-AP, it may be noteworthy that the maximum local concentration achieved by the dose of 5 μg/h was very close to the maximal plasma level achieved with tolerable systemic infusions of the drug. The dose of 5 μg/h was derived from preceding toxicology studies in dogs, where the long-term infusion of 4-AP was examined and 5 μg/h was determined to be the maximal safe dose. Even this dose clearly raised the local excitability of the spinal cord in the patients, leading to significantly decreased reflex thresholds, and at times to direct muscle fasciculation. It seems possible that this kind of excitability change over a prolonged period of time might be at a threshold to affect the viability of neural tissue.

An earlier study in an animal model of spinal cord injury[18] showed that the threshold for effects of 4-AP on conduction in chronically injured mammalion axons was between 50 and 100 ng/ml, though maximal effect was seen at around 1000 ng/ml. On this basis, it seems essential to re-examine the potential beneficial effects of intrathecal delivery in a cohort of patients that have demonstrated clinical benefit from system administration of the drug, to see if higher local doses might yield greater response, as would be expected by extrapolation from the preclinical data.

Acknowledgments

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