

**A. INGREDIENT NAME:**

**AMINOPYRIDINE**

**B. Chemical Name:**

Amino-4 Pyridine, Fampridina. 4-Aminopyridine; 4-Pridinamine

**C. Common Name:**

Gamma-Aminopyridine, P-Aminopyridine, P-Aminopyridine (DOT), 4-AP, Avitrol, Avitrol 200, 4-Pyridylamine, 4-Pyridinamine, Fampridine

**D. Chemical grade or description of the strength, quality, and purity of the ingredient:**

Assay: 99.3%

**E. Information about how the ingredient is supplied:**

White crystals, or crystalline powder, odorless.

**F. Information about recognition of the substance in foreign pharmacopeias:**

**G. Bibliography of available safety and efficacy data including peer reviewed medical literature:**

Agoston, S. Antagonism of ketamine-diazepam anaesthesia by 4-Aminopyridine in human volunteers. *Br J Anaesth*, 1980; 52: 367-370.

Evenhuis, J. Pharmacokinetics of 4-aminopyridine in human volunteers. *Br J Anaesth*, 1981; 53: 567-569.

Ter Wee, P. M. 4-Aminopyridine and haemodialysis in the treatment of verapamil intoxication. *Hum toxicol*, 1985;4:327-329.

Agoston, S. Effects of 4-aminopyridine in Eaton Lambert syndrome. *Br. J Anaesth*, 1978; 50: 383-385.

1998 - 3454 BL-02 - 14 - BDL01

Hayes, K. C., Blight, A. R., and Potter, P. J. Preclinical trial of 4-aminopyridine in patients with chronic spinal cord injury. *Paraplegia*, 1993; 31: 216-224.

Hayes, K. C., Potter, P. J., and Wolfe, D. L. 4-aminopyridine-sensitive neurologic deficits in patients with spinal cord injury. *J Neurotrauma*, 1994; 11(4): 433-446.

**H. Information about dosage forms used:**

Capsules

**I. Information about strength:**

10mg

**J. Information about route of administration:**

Orally

**K. Stability data:**

Melts at about 158.9°  
Strong oxidizing agents  
Strong acids  
Acid chlorides  
Acid Anhydrides

**L. Formulations:**

**M. Miscellaneous Information:**



<1>

Authors

Segal JL. Brunnemann SR.

Title

4-Aminopyridine improves pulmonary function in quadriplegic humans with longstanding spinal cord injury.

Source

Pharmacotherapy. 17(3):415-23, 1997 May-Jun.

Abstract

STUDY OBJECTIVE: To test the hypothesis that 4-aminopyridine (4-AP) might cause clinically evident improvement in pulmonary function in humans with chronic spinal cord injury (chronic SCI). DESIGN: Balanced, open-label study with subjects consecutively enrolled. SETTING: Spinal Cord Injury Service, university-affiliated tertiary level care Department of Veterans Affairs Medical Center. PATIENTS: Seventeen healthy men and women suffering from traumatic SCI (11 quadriplegic, 6 paraplegic patients) for more than 1 year. INTERVENTIONS: Each subject was given a **single dose of 4-AP 10 mg orally in an immediate-release formulation**. MEASUREMENTS AND MAIN RESULTS: Significant increases in mean values of forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), maximal inspiratory pressure (MIP), and **maximal expiratory pressure (MEP) that persisted for at least 12 hours were demonstrated in quadriplegic patients beginning 6 hours after 4-AP administration**. Tests of pulmonary function that demonstrated statistically significant increases at any time were also numerically, if not statistically, increased at 24 hours compared with pretreatment values obtained in 4-AP-naive subjects. CONCLUSIONS: The administration of a single dose of an immediate-release formulation of 4-AP to **humans with longstanding, traumatic quadriplegia is associated with sustained, clinically meaningful, and statistically significant improvements in pulmonary function**. We suggest that the administration of 4-AP may have a salutary effect in patients suffering from SCI and appears to be associated with potentially clinically significant reductions in the pathophysiologic pulmonary sequelae of SCI.

<4>

Authors

Schwid SR. Petrie MD. McDermott MP. Tierney DS. Mason DH. Goodman AD.

Title

Quantitative assessment of sustained-release 4-aminopyridine for symptomatic treatment of multiple

sclerosis.

Source

Neurology. 48(4):817-21, 1997 Apr.

Abstract

**OBJECTIVE:** To evaluate the efficacy of 4-aminopyridine sustained release (4AP SR) (fampridine, EL-970) using quantitative measures of motor function in multiple sclerosis (MS) patients. **BACKGROUND:** In vitro, 4AP improves conduction through demyelinated axons. A previous multicenter trial of 4AP SR using the Expanded Disability Status Scale (EDSS) as the primary outcome was unable to establish clinical efficacy. **DESIGN/METHODS:** Ten MS patients with stable motor deficits (EDSS 6.0-7.5) were given 4AP SR 17.5 mg bid and placebo for 1 week each in a double-blind, placebo-controlled, crossover trial. Time to walk 8 meters, time to climb four stairs, maximum voluntary isometric contraction measured quantitatively (MVICT), manual muscle testing (MMT), grip strength, EDSS, and the patient's global impression were measured. **RESULTS:** Timed gait was improved on 4AP SR compared with placebo in 9 of 10 subjects ( $p = 0.02$ ). Timed stair climbing, MVICT, MMT, grip strength, and EDSS showed nonsignificant improvements on 4AP SR. Based on their global impressions, seven subjects preferred 4AP SR over placebo; only one preferred placebo. There were no serious side effects. **CONCLUSION:** 4AP SR improved motor function in MS patients. The quantitative outcomes used in this study permit more sensitive evaluation of the therapeutic effect and promise to be useful in future trials of symptomatic treatments for MS.

<5>

Authors

Chang FC. Bauer RM. Benton BJ. Keller SA. Capacio BR.

Title

4-Aminopyridine antagonizes saxitoxin- and tetrodotoxin-induced cardiorespiratory depression.

Source

Toxicol. 34(6):671-90, 1996 Jun.

Abstract

Antagonism of saxitoxin- and tetrodotoxin-induced lethality by 4-aminopyridine was studied in urethane-anesthetized guinea pigs instrumented for the concurrent recordings of medullary respiratory-related unit activities (Botzinger complex and Nu. para-Ambiguus), diaphragmatic electromyogram, electrocorticogram, Lead II electrocardiogram, blood pressure, end-tidal CO<sub>2</sub> and arterial O<sub>2</sub>/CO<sub>2</sub>/pH. The toxin (either saxitoxin or

tetrodotoxin) was infused at a dose rate of 0.3 microgram/kg/min (i.v.) to produce a state of progressive cardiorespiratory depression. The animals were artificially ventilated when the magnitude of integrated diaphragm activities was reduced to 50% of control. Immediately after the disappearance of the diaphragm electromyogram, the toxin infusion was terminated, and 4-aminopyridine (2 mg/kg, i.v.) was administered. The therapeutic effect of 4-aminopyridine was striking in that the toxin-induced blockade of diaphragmatic neurotransmission, vascular hypotension, myocardial anomalies, bradycardia and aberrant discharge patterns of medullary respiratory-related neurons could all be promptly restored to a level comparable to that of control condition. The animals were typically able to breathe spontaneously within minutes after 4-aminopyridine. At the dose level used to achieve the desired therapeutic responses, 4-aminopyridine produced no sign of seizure and convulsion. Although less serious side-effects such as cortical excitant/arousal and transient periods of fascicular twitch could be observed, these events were of minor concern, in our opinion, particularly in view of the remarkable therapeutic effects of 4-aminopyridine.

<8>

Authors

Chen HM. Lin CH. Wang TM.

Title

Effects of 4-aminopyridine on saxitoxin intoxication.

Source

Toxicology & Applied Pharmacology. 141(1):44-8, 1996 Nov.

Abstract

Effects of 4-aminopyridine (4-AP) on neurotoxicity induced by saxitoxin (STX) are investigated in this study. In vitro, twitch tension evoked by nerve stimulation was depressed by STX (1.35 nM) in rat phrenic nerve-diaphragm preparations, and this inhibition was antagonized by 4-AP (0.1 mM). In addition, 4-AP (0.1 mM) restored the firing of membrane action potentials that were suppressed or even abolished by 0.334 nM STX in frog sartorius muscles. In vivo studies showed that 4-AP (0.3 mg/kg, iv) significantly reversed the respiratory rate, tidal volume, and blood pressure to normal values in anesthetized STX-toxicosis rats. Furthermore, 4-AP (0.75-6 mg/kg, ip) not only prolonged the survival time but also decreased the mortality of mice (71-43%) at a normally lethal dose (30 micrograms/kg, ip) of STX. The results suggest that 4-AP may be useful as an antidote for STX intoxication.

<11>

Authors

Perez-Espejo MA. Haghigat

Title

The effects of taxol, methylprednisolone, and 4-aminopyridine in compression injury: a qualitative experimental study

Source

Surgical Neurology. 46(4):311-316, 1996.

Abstract

BACKGROUND: Taxol is a diterpenoid that inhibits microtubulin production in cells. It is used in the treatment of cancer, preserving the cytoskeleton of normal cells. The purpose of this study was to evaluate the effects of taxol, methylprednisolone, and 4-aminopyridine on recovery of motor function after spinal cord compression. METHODS: Thirty-nine rats were divided into three groups that received taxol (18 mg/kg), methylprednisolone (30 mg/kg), or 4-aminopyridine (10 mg/kg). Taxol was administered intraperitoneally after injury and two additional doses were given on days 25, 26, and 27. A group of rats served as a control without any treatment. Electrophysiological potentials were recorded before and after injury. Behavioral tests were used to evaluate recovery of motor function. RESULTS: Taxol, methylprednisolone-treated and 4-aminopyridine-treated groups showed significant improvement in recovery of motor function. CONCLUSION: Taxol and methylprednisolone treatment after the compression injury significantly improved recovery of motor function after an incomplete spinal cord injury.

<12>

Authors

Wananukul W. Keyler DE. Pe

Title

Effect of calcium chloride on the toxicity of desipramine in rats

Source

Journal of Toxicology - Clin  
34(5):499-506, 1996.

Abstract

BACKGROUND: Hypotension is a common side effect of tricyclic antidepressants. The purpose of this study was to evaluate the effect of calcium chloride on the toxicity of desipramine in rats.

WinSPIRS 2.1

Usage is subject to the terms and conditions of the subscription and License Agreement and the applicable Copyright and intellectual property protection as dictated by the appropriate laws of your country and/or International Convention.

No.	Records	Request
* 1	10	Wananukul

Record 1 of 1 - MEDLINE EXPRESS (R) 1996

TI: Effect of calcium chloride and 4-aminopyridine therapy on desipramine toxicity in rats.

AU: Wananukul-W; Keyler-DE; Pentel-PR

SO: J-Toxicol-Clin-Toxicol. 1996; 34(5): 499-506

ISSN: 0731-3810

LA: ENGLISH

AB: BACKGROUND: Hypotension is a major contributor to mortality in tricyclic antidepressant overdose. Recent data suggest that tricyclic antidepressants inhibit calcium influx in some tissues. This study addressed the potential role of calcium channel blockade in tricyclic antidepressant-induced hypotension. METHODS: Two interventions were studied that have been shown previously to improve blood pressure with calcium channel blocker overdose. CaCl<sub>2</sub> and 4-aminopyridine. Anesthetized rats received the tricyclic antidepressant desipramine IP to produce hypotension, QRS prolongation, and bradycardia. Fifteen min later, animals received CaCl<sub>2</sub>, NaHCO<sub>3</sub>, or saline. In a second experiment, rats received tricyclic antidepressant desipramine IP followed in 15 min by 4-aminopyridine or saline. RESULTS: NaHCO<sub>3</sub> briefly (5 min) reversed hypotension and QRS prolongation. CaCl<sub>2</sub> and 4-aminopyridine failed to improve blood pressure. The incidence of ventricular arrhythmias (p = 0.004) and seizures (p = 0.03) in the CaCl<sub>2</sub> group was higher than the other groups. CONCLUSION: The administration of CaCl<sub>2</sub> or 4-aminopyridine did not reverse tricyclic antidepressant-induced hypotension in rats. CaCl<sub>2</sub> therapy may possibly worsen both cardiovascular and central nervous system toxicity. These findings do not support a role for calcium channel inhibition in the pathogenesis of tricyclic antidepressant-induced hypotension.

AN: 96393400

WinSPIRS 2.1

Usage is subject to the terms and conditions of the subscription and License Agreement and the applicable Copyright and intellectual property protection as dictated by the appropriate laws of your country and/or International Convention.

No.	Records	Request
1	10	Wananukul
2	224	haghighi
3	224	haghighi
4	2752	4-aminopyridine
* 5	3	haghighi and 4-aminopyridine

Record 1 of 1 - MEDLINE EXPRESS (R) 1991 - 1995

TI: Effect of 4-aminopyridine in acute spinal cord injury.

AU: Haghighi-SS; Pugh-SL; Perez-Espejo-MA; Oro-JJ

SO: Surg-Neurol. 1995 May; 43(5): 443-7

ISSN: 0090-3019

LA: ENGLISH

AB: BACKGROUND: The demyelination process has been proven to be an important factor contributing to long-term sensory and motor impairments after spinal cord injury (SCI). The loss of myelin promotes exposure of K<sup>+</sup> channels in internodal region of the damaged myelinated axons leading to K<sup>+</sup> efflux into the neurons with subsequent blockage of action potentials. The potassium channel blocker 4-aminopyridine (4-AP) has been effective in restoring some sensory and motor impairment in incomplete SCI patients. The effect of this compound given immediately after an acute injury is not known. The objective of this study was to determine if blockage of K<sup>+</sup> ions efflux immediately after an acute SCI would improve neuronal conduction in this model of injury. METHODS: Cortical somatosensory evoked potentials (SSEPs) were recorded before and after a weight-induced compression injury of 120 grams, and were monitored up to 5 hours postinjury. A randomized treatment was initiated with administration of either vehicle or 4-AP. All 4-AP treatments were given as intravenous bolus injections of 1.0, 0.5, and 0.3 mg/kg at 1, 2, and 3 hours after the trauma. RESULTS: The SSEPs were abolished immediately after the injury in all control and treated animals. Both groups showed spontaneous recovery of the SSEPs at the rate of 44.5% for the 4-AP treated and nontreated groups at the second hour postinjury. This recovery rate remained the same for both groups at the end of the experiments. CONCLUSIONS: Based on the recovery of the SSEPs, our data indicate that early administration of 4-AP lacks any beneficial effect on axonal function during acute stage of spinal cord injury.

AN: 95389330

Other 8 AMG rabbits given 3,4-diaminopyridine (3,4-DAP) 0.4 mg.kg-1 showed a similar improvement for 9.3 +/- 3.1 h. These results indicated that 4-AP and 3,4-DAP were effective in treating the AMG in rabbits, they may be useful in the clinical treatment of myasthenia gravis patients.

<29>

Authors

Polman CH. Bertelsmann FW. de Waal R. van Diemen HA. Uitdehaag BM. van Loenen AC. Koetsier JC.

Title

**4-Aminopyridine is superior to 3,4-diaminopyridine in the treatment of patients with multiple sclerosis.**

Source

Archives of Neurology. 51(11):1136-9, 1994 Nov.

Abstract

OBJECTIVE: To compare the efficacy and toxicity of 4-aminopyridine and 3,4-diaminopyridine in patients with multiple sclerosis. DESIGN: Intervention study with a before-after design and a randomized, double-blind, crossover design. SETTING: University referral center. PATIENTS: Twenty-four patients with definite multiple sclerosis who had been treated in a previous clinical trial with 4-aminopyridine. INTERVENTIONS: Nonresponders to treatment with 4-aminopyridine (14 patients) were treated with 3,4-diaminopyridine in a 4-week, open-label trial with doses up to 1.0 mg/kg of body weight (before-after design). Responders to treatment with 4-aminopyridine (10 patients) participated in a comparative study of 6 weeks' duration with 4-aminopyridine and 3,4-diaminopyridine according to a randomized, double-blind, double-crossover design. MAIN OUTCOME MEASURES: Neurophysiologic variables for nonresponders, neurologic functions and symptoms on a visual analogue scale for responders, and side effects for both groups. RESULTS: Toxicity profiles of 4-aminopyridine and 3,4-diaminopyridine were different, and systemic tolerability was reduced for 3,4-diaminopyridine. 4-Aminopyridine was more effective than 3,4-diaminopyridine, especially for ambulation, fatigue, and overall daily functioning. CONCLUSION: Our data suggest that, concerning both efficacy and side effects, 4-aminopyridine is superior to 3,4-diaminopyridine in the treatment of patients with multiple sclerosis.

<30>

Authors

Smits RC. Emmen HH. Bertelsmann FW. Kulig BM. van Loenen AC. Polman CH.

Title

The effects of 4-aminopyridine on cognitive function in patients with multiple sclerosis: a pilot study.

Source

Neurology. 44(9):1701-5, 1994 Sep.

Abstract

4-Aminopyridine (4-AP) has a favorable effect on the disability of certain patients with MS. We investigated the effect of 4-AP on neuropsychological performance in 20 MS patients using a randomized, double-blind, placebo-controlled, crossover design. Although there was a trend for improved performance with 4-AP for two of the tests, we could not demonstrate significant effects of 4-AP on cognitive function.

<32>

Authors

Bever CT Jr.

Title

The current status of studies of aminopyridines in patients with multiple sclerosis. [Review] [29 refs]

Source

Annals of Neurology. 36 Suppl:S118-21, 1994.

Abstract

Because the symptomatic treatments for multiple sclerosis (MS) are limited, new approaches have been sought. Anatomical studies of MS lesions show a relative preservation of axons, and clinical studies suggest that some of the neurological impairment in patients with MS is physiological. Electrophysiological studies suggest that demyelination exposes axonal potassium channels that decrease action-potential duration and amplitude, hindering action-potential propagation. Potassium channel blockers, including aminopyridines, have been shown to improve nerve conduction in experimentally demyelinated nerves. Two potassium channel blockers, 4-aminopyridine (AP) and 3,4-diaminopyridine (DAP) have been tested in patients with MS. Preliminary studies of AP demonstrated benefit in many temperature-sensitive patients with MS, and improvement of function was found in a large randomized double-blind, placebo-controlled crossover trial of 3 months of oral treatment in 68 patients with MS. An open-label trial of DAP showed improvement in some deficits, and a double-blind placebo-controlled trial showed significant improvements in prospectively defined neurological deficits. A crossover comparison of the two agents suggested that AP produces



## **4-AMINOPYRIDINE**

Rodent oral LD50 is approx. 20 mg/kg. Long term toxicity has not been thoroughly investigated.

It is an eye, skin, respiratory and G.I. tract irritant and has caused aspiration toxicities. It can be absorbed through the skin and has caused nausea, vomiting, hallucinations, seizures, and distorted perceptions. May cause hepatitis, has caused dizziness, elevations in body temperature, anxiety and paresthesias.

Used to treat Multiple Sclerosis and is antidotal in poisonings with tetrodotoxin, saxitoxin (non-depolarizing muscle relaxants) and calcium channel blockers.



## REFERENCES

1. Segal JL, Brunnemann SR. 4-Aminopyridine improves pulmonary function in quadriplegic humans with longstanding spinal cord injury. *Pharmacotherapy* 1997; 17(3):415-23.
2. Schwid SR, Petrie MD, McDermott MP, et al. Quantitative assessment of sustained-release 4-aminopyridine for symptomatic treatment of multiple sclerosis. *Neurology* 1997; 48(4):817-21.
3. Chang FC, Bauer RM, Benton BJ, et al. 4-Aminopyridine antagonizes saxitoxin- and tetrodotoxin-induced cardiorespiratory depression. *Toxicol* 1996; 34(6):671-90.
4. Chen HM, Lin CH, Wang TM. Effects of 4-aminopyridine on saxitoxin intoxication. *Toxicology & Applied Pharmacology* 1996; 141(1):44-8.
5. Perez-Espejo MA, Haghighi SS, Adelstein EH, et al. The effects of taxol, methylprednisolone, and 4-aminopyridine in compressive spinal cord injury: a qualitative experimental study. *Surgical Neurology* 1996; 46(4):350-7.
6. Wananukul W, Keyler DE, Pentel PR. Effect of calcium chloride and 4-aminopyridine therapy on desipramine toxicity in rats. *Journal of Toxicology- Clinical Toxicology* 1996; 34(5):499-506.
7. Pickett TA, Enns R. Atypical presentation of 4-aminopyridine overdose. *Annals of Emergency Medicine* 1996; 27(3):382-5.
8. Haghighi SS, Pugh SL, Perez-Espejo MA, et al. Effect of 4-aminopyridine in acute spinal cord injury. *Surgical Neurology* 1995; 43(5):443-7.
9. Hayes KC, Potter PJ, Wolfe DL, et al. 4-Aminopyridine-sensitive neurologic deficits in patients with spinal cord injury. *Journal of Neurotrauma* 1994; 11(4):433-46.
10. Li L, Zhang YP. [Therapy of experimental autoimmune myasthenia gravis in rabbits with 4-aminopyridine and 3,4-diaminopyridine]. [Chinese] *Chung-Kuo Yao Li Hsueh Pao- Acta Pharmacologica Sinica* 1994; 15(4):358-62.
11. Polman CH, Bertelsmann FW, de Waal R, et al. 4-Aminopyridine is superior to 3,4-diaminopyridine in the treatment of patients with multiple sclerosis. *Archives of Neurology* 1994; 51(11):1136-9.
12. Smits RC, Emmen HH, Bertelsmann FW, et al. The effects of 4-aminopyridine on cognitive functions in patients with multiple sclerosis: a pilot study. *Neurology* 1994; 44(9):1701-5.
13. Bever CT Jr. The current status of studies on aminopyridines in patients with multiple sclerosis. [Review] [29 refs] *Annals of Neurology* 1994; 36 Suppl S1 18-21.
14. Bever CT Jr, Young D, Anderson PA, et al. The effects of 4-aminopyridine in multiple sclerosis patients: results of a randomized, placebo-controlled, double-blind, concentration-controlled, crossover trial. *Neurology* 1994; 44(6):1054-9.
15. Polman CH, Bertelsmann FW, van Loenen AC, et al. 4-aminopyridine in the treatment of patients with multiple sclerosis. Long-term efficacy and safety. *Archives of Neurology* 1994; 51(3):292-6.
16. Van Dieman HA, Polman CH, van Dongen MM, et al. 4-Aminopyridine induces functional improvement in multiple sclerosis patients: a neurophysiological study. *Journal of the Neurological Sciences* 1993; 116(2):220-6.

17. Hansebout RR, Blight AR, Fawcett S, et al. 4-Aminopyridine in chronic spinal cord injury: a controlled, double-blind, crossover study in eight patients [see comments]. *Journal of Neurotrauma* 1993; 10(1):1-18.
18. Hayes KC, Blight AR, Potter PJ, et al. Preclinical trial of 4-aminopyridine in patients with chronic spinal cord injury. *Paraplegia* 1993; 31(4):216-24.
19. Van Dieman HA, van Dongen MM, Dammers JW, et al. Increased visual impairment after exercise (Uhthoff's phenomenon) in multiple sclerosis: therapeutic possibilities. *European Neurology* 1992; 32(4):231-4.
20. van Dieman HA, Polman CH, van Dongen MM, et al. The effect of 4-aminopyridine on clinical signs in multiple sclerosis: a randomized, placebo-controlled, double-blind, cross-over study. *Annals of Neurology* 1992; 32(2):123-3.
21. Nockels R, Young W. Pharmacological strategies in the treatment of experimental spinal cord injury. [Review] [27 refs] *Journal of Neurotrauma* 1992; 9Suppl 1:S211-7.
22. Stefoski D, Davies FA, Fitzsimmons WE, et al. 4-Aminopyridine in multiple sclerosis: prolonged administration. *Neurology* 1991; 41(9):1344-8.
23. Blight AR, Toombs JP, Bauer MS, et al. The effects of 4-aminopyridine on neurological deficits in chronic cases of traumatic spinal cord injury in dogs: a phase I clinical trial. *Journal of Neurotrauma* 1991; 8(2):103-19.
24. Wiseman EJ, Jarvik LF. Potassium channel blockers: could they work in Alzheimer disease?. [Review] [38 refs] *Alzheimer Disease & Associated Disorders* 1991; 5(1):25-30.
25. Davis FA, Stefoski D, Rush J. Orally administered 4-aminopyridine improves clinical signs in multiple sclerosis [see comments]. *Annals of Neurology* 1990; 27(2):186-92.