



DIAMINOPYRIDINE TREATMENT OF NEUROLOGICAL DISORDERS

Monday, March 17, 2003

Wise Young, Ph.D., M.D.

W. M. Keck Center for Collaborative Neuroscience
Rutgers University, Piscataway, New Jersey 08540-8082

Email: wisey@pipeline.com, <http://sciwire.com>

Summary: The drug 3, 4 diaminopyridine (DAP) is a potassium channel blocker, closely related to 4-aminopyridine. Like 4-AP, DAP blocks the voltage-sensitive potassium channel. However, unlike 4-AP, DAP does not cross the blood brain barrier unless the barrier is broken. DAP therefore should be well suited for treating peripheral demyelination and have less central nervous system mediated side-effects. Many clinical studies of DAP suggest that DAP effectively relieves the symptoms of Lambert-Eaton myasthenia syndrome (LEMS). However, DAP has limited or questionable efficacy for other conditions such as botulinum toxin poisoning, Guillian-Barre, polyneuropathy, myasthenia gravis, and multiple sclerosis, or botulinum toxicity. There is little published data regarding the efficacy of DAP on brain or spinal cord injury. The side-effects of DAP appears to be similar to 4-AP except that it causes more peripheral symptoms. Several cases of seizures have been reported, as well as one incident of cardiac arrest. Otherwise, the drug appears to be well-tolerated in all the clinical trials to date. This article reviews some of the medical literature relating to the use of DAP to treat various neurological disorders.

Use of DAP to treat Lambert-Eaton Myasthenia Syndrome

Clinicians have used DAP to treat patients with Lambert-Eaton Myasthenia Syndrome (LEMS) for over 20 years. LEMS is a rare disorder of neuromuscular transmission that is often associated with pulmonary carcinoma.

- Newsom-Davis (2001) reviewed the more recent literature on treatment of LEMS and concluded that weakness and autonomic dysfunction in this condition can be “partially or fully controlled by 3,4-Diaminopyridine”.
- Sanders, et al. (2000) carried out a randomized trial of DAP in LEMS. Twenty-six patients completed the trial, receiving 20 mg of DAP or placebo three times daily. All but one of the patients had significant symptomatic improvement with no evidence of side-effects.

- Oishi, et al. (2001) examined the effects of DAP on motor function in a 72-year old woman with LEMS. She had weakness and atrophy of the thigh muscles. DAP markedly improved her quadriceps strength and her ability to climb stairs.
- Itoh, et al. (2001) treated a 72-year old man with LEMS with DAP and showed that he had a stronger hand grip.
- Tim, et al. (2000) reports the effects of DAP on 72 patients with LEMS, showing that DAP treatment doubled muscle action potential amplitudes in 41% of 53 patients and that 79% had marked self-reported functional improvement.
- Satoh, et al. (2001) reported that DAP reduced symptoms of neurogenic bladder in a patient with LEMS.
- Kanzato, et al. (1999) reported that DAP reduced ocular abnormalities in a patient with LEMS.
- Maddison, et al. (1998) found that DAP increased compound action potential amplitudes measured from the little finger of 6 patients with LEMS.
- Molgo & Guglielmi (1996) reviewed the literature and suggested that DAP used either alone or in conjunction with other therapies is beneficial for both motor and autonomic deficits in patients with primary or paraneoplastic LEMS. The clinical reports suggest that about 150 myasthenic patients world-wide had been treated with DAP and that it is well tolerated.
- Smith & Wald (1996) used DAP to treat acute ventilatory failure in a patient with LEMS, showing beneficial effects.
- Lundh, et al. (1993) gave DAP for over 10 years to 19 patients with LEMS.
- Tsuchiya, et al. (1993) reported beneficial effects of DAP in a 65-year old woman with LEMS associated with Sjogren's syndrome and discoid lupus erythematosus.
- Jost, et al. (1992) gave DAP for over 12 months to a patient with LEMS, showing that this produced an objective increase in muscle power with no increase in muscle weakness. Withdrawal of the drug resulted in greater weakness, suggesting that the treatment ameliorated the symptoms but does not prevent disease progression during the treatment period.
- Palace, et al. (1991) did an open prospective trial and showed that DAP markedly increased muscle strength in 6 patients with LEMS, followed by a double-blind crossover trial with 4 patients. In the open trial, 13 of 16 patients showed improvement. In the randomized crossover trial, 4 of 4 patients showed no effect.
- Lund, et al. (1984) found that intravenous, oral, and rectal administration of DAP in five LEMS patients showed clinical improvements of neuromuscular and autonomic function without severe side effects. Anticholinesterase drugs are synergistics with the beneficial effects of DAP in LEMS.

In summary, much evidence indicate both the safety and efficacy of DAP for treatment of LEMS, both alone and in combination with other drugs. The drug produces marked symptomatic improvements in motor strength and relief of autonomic symptoms in 5-80% of patients. The drug appears to be well-tolerated in oral doses of up to 80 mg per day. Although the drug does not appear to change the progressive course of the diseases, it has been used for decades with no significant loss of efficacy or hepatic or renal toxicity.

DAP Treatment of Other Neurological Disorders

DAP has also been used to treat amyotrophic lateral sclerosis (ALS), myasthenia gravis, multiple sclerosis (MS), and chronic demyelinating polyneuropathy but without convincing evidence of efficacy.

- *Amyotrophic lateral sclerosis.* Aisen, et al. (1996) used DAP to treat amyotrophic lateral sclerosis because DAP should increase the amount of neurotransmitter release and thereby increase the efficacy of remaining synaptic connections. They gave a single dose (10-80 mg) or placebo and measured function, strength, spasticity, nerve conduction, and speech. They found a statistically significant improvement in function and speech during hospitalization but no significant differences in clinical or electrophysiological measures between DAP and placebo.
- *Multiple Sclerosis.* Bever, et al. (1996) used DAP to treat 28 patients with MS in a double-blind crossover trial. They gave doses up to 100 mg per day and found that the DAP improved neurologic deficits in 22 of the patients during DAP treatment but only 2 of the patients during placebo. Bever, et al. (1994) carried out an open-label trial of 4-AP and DAP in 68 patients with MS. DAP seems to have improved function. The toxicity profile differed. AP produced more central nervous system side-effects while DAP produced more peripheral side effects such as paresthesias and abdominal pain. Polman, et al. (1994) assessed efficacy and toxicity of DAP in 24 patients with MS and who had previously been treated with 4AP. In a randomized, double-blinded crossover trial, they found that 4-AP was more effective than DAP, especially for ambulation, fatigue, and overall daily functioning. Solari, et al. (2001) reviewed the literature on clinical trials assessing aminopyridine treatments of MS. Five double-blind, single center, crossover trials were identified, involving 144 participants treated with either 4-AP or DAP. One 6 adverse responses were noted: one acute encephalopathy, 3 episodes of confusion, and two seizures. Sheean, et al. (1998) did an open-labeled clinical and electrophysiological study of DAP in 8 patients with multiple sclerosis. Six of the eight patients reported substantial improvement in fatigue. However, electrophysiological tests revealed no differences.
- *Myasthenia gravis.* Anlar, et al. (1996) used DAP in a double-blind randomized placebo-control trial to assess the effects of DAP on eleven patients with congenital and five with juvenile myasthenia gravis (a muscle wasting disease). The juvenile patients did not respond. Five of the 11 patients with congenital myasthenia treated with DAP showed positive responses but so did 3 of the 11 patients that received placebo. The authors emphasized the importance of placebo-controlled trials. The number of patients is too small to yield convincing evidence for or against DAP effect in myasthenia gravis.
- *Demyelinating Polyneuropathy.* Russell, et al. (1995) carried out a placebo-controlled randomized crossover trail of 34 patients with stable chronic demyelinating polyneuropathy. These ranged from hereditary motor and sensory neuropathy in 27 patients and the remainder had acquired demyelinating polyneuropathy. Daily doses of 20 mg four times per day produced a small but significant improvement in Neurological Disability Score but no improvements were noted in any of the other neurological measures. The authors conclude that the treatment is unlikely to be beneficial in the treatment of this condition. Bergin, et al.

(1993) gave a single oral dose of DAP to 6 patients with inflammatory demyelinating neuropathies including Guillian-Barre and chronic inflammatory demyelinating neuropathy. They did not find improvement in conduction or clinical benefit from the treatment.

- *Botulinism.* DAP has been reported to be useful for treating botulinum toxin poisoning in animals but several anecdotal cases suggest that it is not as consistently effective in reversing botulinum toxin poisoning and other kinds of toxins in humans. Dock, et al. (2002) reports a case where DAP markedly improved a patient who had botulinum toxin poisoning due to oral ingestion of the toxin. This is consistent with a substantial literature suggesting that 4-AP also has beneficial effects of this condition and other neural toxins that affect the neuromuscular junction. Like 4-AP, DAP should increase the amount of acetylcholine released per action potential at the neuromuscular junction. Davis, et al. (1992) gave DAP in a double-blind randomized, placebo-controlled trial in a 31-year old patient with severe food-borne type A botulism poisoning and did not observe any benefits. Trevett, et al. (1995) used DAP and edrophonium to treat a patient after the bite of the Papuan taipan but found that either or both together were insufficient to provide significant clinical benefit.

In summary, DAP appears to be less effective for a variety of other neurological disorders, including ALS and MS. Surprisingly, DAP appears to have little effect on peripheral demyelination conditions. There is insufficient data to rule in or out beneficial effects of the drug on myasthenia gravis or botulinum toxin poisoning.

Side Effects of DAP

In the published literature, several hundred patients have received DAP in doses ranging from 10-20 mg four times per day. Most of the studies suggest that the side-effects of DAP are similar to those of 4-AP, including headache, fatigue, perioral and/or distal paraesthesia 30-60 minutes after a dose, and difficulty sleeping. Paresthesias and abdominal discomfort occur in most patients (Bever, et al. 1990). Excessive doses of DAP can lead to seizures and the drug is therefore contraindicated in patients with a history of epilepsy. Laboratory studies indicate no evidence of DAP toxicity affecting liver, renal, hematological, endocrinologic, or electrocardiologic function acutely or after 6 months of DAP treatment (Sanders, et al. 2000).

In theory, DAP should have less side-effects than 4-AP because it does not penetrate the blood brain barrier. Rat studies (Lemeignan, et al., 1984; Damsma, et al., 1988) suggest that DAP penetrates the blood brain barrier much less than 4-AP. However, the side-effects of DAP have been remarkably similar to 4-AP in patients with 4-AP in MS. This may be related to breaches of the blood brain barrier during acute exacerbating MS episodes (Greenwood, et al., 2003; Petty & Lo, 2002; Rosenberg, et al., 2002; Proescholdt, et al., 2002). The side-effects of DAP on MS may therefore depend on the presence of active neuroinflammatory disease and openings of the blood brain barrier. Although Bevers, et al. (1994, 1996) reported beneficial effects of DAP in patients with MS, 8 of 36 patients withdrew from the study due to side effects.

Some side-effects from DAP may be related to the high doses used in the trials. Clinical trials often gave oral doses of 80-100 mg of DAP per day while oral doses of 4-AP are usually limited to 40-60 mg per day. Polman, et al. (1994) compared toxicity of DAP and 4-AP up to oral doses of 1 mg/kg per day in 24 patients with multiple sclerosis; 4-AP was more effective in improving ambulation, fatigue, and overall daily function than DAP and patients had less systemic tolerability for DAP than 4-AP. Long term treatment of 31 patients with multiple sclerosis for 6-32 months, using daily doses of 0.5 mg/kg per day, was associated with only three major adverse events: two patients with generalized epileptic seizure and one with hepatitis (Polman, et al., 1994). Rossini, et al. (2001) reported “no relevant side effects” of 4-AP in 54 multiple sclerosis patients who received 32 mg per day orally for 6 months to treat fatigue. Drug responders had >30 ng/ml 4-AP blood levels. In 20 patients with chronic incomplete spinal cord injury, daily doses of 4-AP up to 0.5 mg/kg per day did not produce significant side-effects (van der Bruggen, et al. 2001). Likewise, Potter, et al. (1998) treated 26 patients with chronic spinal cord injury for 2 weeks with 12.5 and 17.5 mg twice a day with a sustained release version of 4-aminopyridine (Fampridine SR) and found only transient and “trivial” episodes of lightheadedness and nausea. Potter, et al. (1998) assessed 10 mg of 4-AP given 2-3 times per day in 3 patients, finding no evidence of renal or hepatic toxicity.

To distinguish between “central” and “systemic” effects of 4-AP, Halter, et al. (2000) gave 4-AP intrathecally at 5 micrograms/hour for 4-5 hours to 6 patients with chronic spinal cord injury and found no systemic side effects. Pratt, et al. (1995) had earlier given 1-60 micrograms per hour of 4-AP intrathecally to dogs and did not observe any systemic symptoms except for a mild hindlimb tremor that reversed with reduction or termination of drug delivery. In contrast, Donovan, et al. (2000) gave 30 mg of 4-AP intravenously over two hours to 12 paraplegic patients, observing penetration of 4-AP into cerebrospinal fluid. Many of the patients in this study complained of “unpleasant symptoms” during the 4-AP infusion and the authors concluded that intravenous administration of 4-AP “may not be the best way to administer this drug”. Hayes, et al. (1994) gave 24-25 mg total dose at 6 or 15 mg/hour intravenously to 6 patients and found that 4-AP markedly increased cortical somatosensory evoked potentials in 2 patients and increased motor evoked potentials in 4 patients, associated with improved voluntary motor unit recruitment. Bever, et al. assessed the effects of intravenous 4-AP achieving 30-59 ng/ml and 60-100 ng/ml serum levels and reported that all patients experienced side effects of at the higher serum levels; one patient had a grand mal seizure at 104 ng/ml and another had an acute confusional episode at 114 ng/ml.

Few cases of 4-AP or DAP poisoning have been reported. Spyker, et al. (1980) reported seizures associated with acute 4-AP poisoning in three adult males. One case of acute poisoning with 4-AP has been reported in an 8-month old infant (Velez, et al., 2003), resulting in opisthotonic posturing and neuromuscular irritation. Pickett & Enns (1996) reported one case of 4-AP overdose that caused continuous dystonic, choreoathetoid-type movements that responded to benzodiazepines. Smeets & Kunst (1995) reported a 22-year old weight lifter who overdosed with 4-AP, raising his plasma level of 335 ng/ml and producing epileptic seizures and confusion, cardiac arrhythmias, conduction disorders, and severe hypertension. One case of cardiac arrest associated with DAP intoxication has been reported (Boerma, et al., 1995).

In summary, in higher doses of 80-100 mg per day, oral DAP appears to have many side-effects, including headache, fatigue, paresthesias, and abdominal pain. In theory, DAP should have less side effects than 4-AP because DAP does not penetrate as well across the blood brain barrier and should produce less central side-effects such as epileptic seizures or confusion. At doses of 40-60 mg per day, oral DAP and 4-AP both seem to have minimal side-effects. DAP appears to be safe for long term use. It has been used for more than 2 decades to treat patients with LEMS and no adverse toxicity has been reported even after years of therapy.

References Cited

- Aisen ML, Sevilla D, Edelstein L and Blass J (1996). A double-blind placebo-controlled study of 3,4-diaminopyridine in amyotrophic lateral sclerosis patients on a rehabilitation unit. *J Neurol Sci* **138**:93-6. Summary: 3,4-Diaminopyridine (DAP) enhances acetylcholine release from the nerve terminal and improves conduction in demyelinated axons. In this double-blinded placebo controlled cross over study we examined the effects of DAP combined with inpatient rehabilitation in nine patients with disabling motor weakness due to amyotrophic lateral sclerosis (ALS). A single dose of DAP or placebo was increased daily to the maximum (range: 10-80 mg) tolerated dose; after patients were assessed on the first treatment, the alternate drug was given in the same manner. Functional Independence Measurement (FIM), Ashworth, grip strength, limb strength measurements, nerve conduction studies and speech assessments were initiated 1/2 h after receiving the maximum tolerated dose of DAP or placebo. DAP was tolerated in all patients, but limited by gastrointestinal side effects in four patients. The mean peak serum level was 20.11 (S.D. = 5.11) ng/ml, occurring 1.25 (S.D. = 0.56) h after dose. A statistically significant improvement in FIM and speech assessment scores between admission and discharge occurred. However, no significant differences in clinical or electrophysiologic measures were seen between DAP and placebo treatments. This study suggests that intensive inpatient rehabilitation has a role in the management of patients with ALS, but DAP does not diminish motor impairment. Burke Rehabilitation Center, White Plains, NY 10605, USA.
- Anlar B, Varli K, Ozdirim E and Ertan M (1996). 3,4-diaminopyridine in childhood myasthenia: double-blind, placebo-controlled trial. *J Child Neurol* **11**:458-61. Summary: Eleven patients with congenital and five with juvenile myasthenia gravis, aged 5 to 24 years, were given 3,4-diaminopyridine in a double-blind, placebo-controlled, crossover study. Clinical improvement was observed in 5 of 11 congenital myasthenia patients, and placebo effect, in 3 of 11. Juvenile myasthenia patients did not respond. Single-fiber electromyographic studies did not reveal any changes correlating with the clinical status of the patient. This study demonstrates the importance of double-blind and placebo-controlled studies to determine the effect of 3,4-diaminopyridine in congenital myasthenia. This drug may have different effects on various presynaptic and postsynaptic defects of neuromuscular transmission resulting in congenital myasthenia syndromes. Department of Pediatric Neurology, Hacettepe University, Ankara, Turkey.
- Bergin PS, Miller DH, Hirsch NP and Murray NM (1993). Failure of 3,4-diaminopyridine to reverse conduction block in inflammatory demyelinating

neuropathies. *Ann Neurol* **34**:406-9. Summary: 3,4-Diaminopyridine was administered to 6 patients with inflammatory demyelinating neuropathies in whom partial conduction block was demonstrable. Four had Guillain-Barre syndrome and 2 had chronic inflammatory demyelinating neuropathy. Nerve conduction studies were performed before the administration of a single oral dose of 3,4-diaminopyridine, and at regular intervals thereafter. Neither resolution of conduction block nor clinical benefit were seen. National Hospital for Neurology and Neurosurgery, London, United Kingdom.

- Bever CT, Jr., Anderson PA, Leslie J, Panitch HS, Dhib-Jalbut S, Khan OA, Milo R, Hebel JR, Conway KL, Katz E and Johnson KP (1996). Treatment with oral 3,4 diaminopyridine improves leg strength in multiple sclerosis patients: results of a randomized, double-blind, placebo-controlled, crossover trial. *Neurology* **47**:1457-62. Summary: To examine the efficacy and toxicity of oral 3,4 diaminopyridine (DAP) in dosages up to 100 mg/day, 36 patients with multiple sclerosis (MS) enrolled in a randomized, double-blind, placebo-controlled, crossover trial. The primary outcome measure was improvement of a prospectively defined neurologic deficit, which was leg weakness in 34 patients. Secondary outcome measures included the patient's subjective response, scored manual motor testing (MMT) of leg strength, scored leg strength from videotaped motor testing (VMT), quadriceps and hamstrings strength (QMT) measured by isometric dynamometry, neuropsychological testing (NPT), ambulation index (AI), and Expanded Disability Status Scale (EDSS) score. Paresthesias and abdominal pain were common and were dose limiting in eight patients. Three patients had episodes of confusion, and one patient had a seizure while on DAP. Eight patients withdrew from the study, leaving 28 evaluable patients for the efficacy analysis. The prospectively defined neurologic deficit improved in 24 patients-22 on DAP and 2 on placebo ($p = 0.0005$). All improvements were in leg weakness. Subjective response and measures of leg strength and function (MMT, VMT, QMT, and AI) improved on DAP compared with placebo. Neither NPT nor EDSS scores improved. DAP treatment can induce improvements in leg strength in MS patients, but toxicity is limiting in many patients. Department of Neurology, School of Medicine, University of Maryland, Baltimore, USA.

- Bever CT, Jr. (1994). The current status of studies of aminopyridines in patients with multiple sclerosis. *Ann Neurol* **36 Suppl**:S118-21. Summary: 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 more central nervous system side effects (dizziness and confusion), whereas DAP produces more peripheral side effects (paresthesias and abdominal pain). Both agents have rarely caused seizures. These studies suggest that aminopyridines may provide a new approach to the symptomatic treatment of MS. Department of Neurology, University of Maryland School of Medicine, Baltimore.

- Bever CT, Jr., Young D, Anderson PA, Krumholz A, Conway K, Leslie J, Eddington N, Plaisance KI, Panitch HS, Dhib-Jalbut S and et al. (1994). The effects of 4-aminopyridine in multiple sclerosis patients: results of a randomized, placebo-controlled, double-blind, concentration-controlled, crossover trial. *Neurology* **44**:1054-9. Summary: Because 4-aminopyridine (AP) improves residual deficits in some multiple sclerosis (MS) patients but has a narrow toxic-to-therapeutic margin, we compared the safety and efficacy of two target peak serum concentration ranges (low: 30 to 59 ng/ml and high: 60 to 100 ng/ml). We enrolled eight MS patients with temperature-sensitive visual and motor deficits in a randomized, placebo-controlled, double-blind, crossover trial of short-term oral AP treatment. We randomized patients to a sequence of three treatments on three separate days: placebo, low serum concentration, and high serum concentration. We determined dosing to achieve the desired steady-state peak serum concentration ranges from a test dose and population pharmacokinetic parameters using bayesian estimation. Contrast sensitivity, standard neurologic examination, ratings of videotaped neurologic examinations, and quantitative strength assessment all improved with treatment, but flicker fusion frequency, visual evoked response latencies, and Expanded Disability Status Scale scores did not. All patients experienced side effects during the high-serum-concentration arm. A grand mal seizure occurred at a serum AP level of 104 ng/ml, and an acute confusional episode occurred at 114 ng/ml. AP treatment produced improvements in residual deficits in MS patients, but the occurrence of significant toxicity suggests that AP serum levels should be monitored and peak levels above 100 ng/ml should be avoided. Concentration-control methodology may be useful in testing putative treatments for other neurologic diseases. Department of Neurology, University of Maryland Hospital, Baltimore 21201.

- Bever CT, Jr., Leslie J, Camenga DL, Panitch HS and Johnson KP (1990). Preliminary trial of 3,4-diaminopyridine in patients with multiple sclerosis. *Ann Neurol* **27**:421-7. Summary: Ten patients with multiple sclerosis (MS) were enrolled in a preliminary trial of the potassium channel blocker, 3,4-diaminopyridine, to evaluate drug toxicity and pharmacokinetics. The patients were treated with oral 3,4-diaminopyridine, first with increasing single doses up to 100 mg and then with divided dosage for up to 3 weeks. Paresthesias were reported by all patients and abdominal pain was dose limiting in 6 patients. 3,4-Diaminopyridine levels and half-life varied widely from patient to patient. Cerebrospinal fluid levels of 3,4-diaminopyridine were about 10% of those in serum. Neither seizures nor epileptiform changes on electroencephalographic examination occurred. Small reversible improvements in specific neurological deficits were seen on examination in all patients and reversible improvement in visual evoked response latencies were found in 2 patients. These results suggest that further study of 3,4-diaminopyridine in patients with MS is warranted. Department of Neurology, School of

Medicine, University of Maryland, Baltimore.

- Boerma CE, Rommes JH, van Leeuwen RB and Bakker J (1995). Cardiac arrest following an iatrogenic 3,4-diaminopyridine intoxication in a patient with Lambert-Eaton myasthenic syndrome. *J Toxicol Clin Toxicol* **33**:249-51. Summary: Syndromes with impaired neuromuscular transmission are frequently treated with pyridine derivatives. 3,4-diaminopyridine is thought to have fewer side effects than the commonly used, but less potent, 4-aminopyridine. We describe a patient with an initially unrecognized iatrogenic intoxication with 3,4-diaminopyridine. Except for a life threatening arrhythmia, symptoms were similar to a 4-aminopyridine intoxication. The patient made a full recovery with symptomatic treatment and withdrawal of the drug. Lukas Hospital Apeldoorn, The Netherlands.
- Damsma G, Biessels PT, Westerink BH, De Vries JB and Horn AS (1988). Differential effects of 4-aminopyridine and 2,4-diaminopyridine on the in vivo release of acetylcholine and dopamine in freely moving rats measured by intrastriatal dialysis. *Eur J Pharmacol* **145**:15-20. Summary: The central effects of 4-aminopyridine (4-AP), a blocking agent of voltage-dependent potassium channels, and its more polar analogue, 2,4-diaminopyridine (2,4-DAP), were studied after i.p. injection and direct intrastriatal administration in rats. The effects of the drugs on the release of acetylcholine (ACh) and dopamine (DA) were quantified by means of an in vivo microdialysis sampling technique. Both neurotransmitters were determined by on-line HPLC analysis. Both aminopyridines increased the release of ACh dose dependently when administered intrastriatally. After peripheral administration, however, 4-AP but not 2,4-DAP induced an increase in the release of ACh. These results are interpreted as being due to the greater lipid solubility of 4-AP compared to 2,4-DAP and hence its better penetration through the blood-brain barrier. Intrastriatal administration of 4-AP induced a much lower increase in the release of DA compared to ACh, whereas there was no change in the release of DA after peripheral administration. These results indicate that the sensitivity of excitable membranes to the releasing effects of 4-AP is not the same for DA- and ACh-containing neurotransmitter systems. Department of Medicinal Chemistry, University of Groningen, The Netherlands.
- Davis LE, Johnson JK, Bicknell JM, Levy H and McEvoy KM (1992). Human type A botulism and treatment with 3,4-diaminopyridine. *Electromyogr Clin Neurophysiol* **32**:379-83. Summary: 3,4-diaminopyridine was evaluated for its ability to improve muscle strength, respiratory function and electromyographic compound muscle action potentials in human botulism. In a double blind, placebo controlled study, 3,4-diaminopyridine failed to improve these parameters in a 31-year old patient with severe food-borne type A botulism. The addition of an anti-cholinesterase medication to the 3,4-diaminopyridine did not add any benefit. Lack of clinical improvement from 3,4-diaminopyridine in this patient differed from some reports of benefit in animals experimentally poisoned with type A botulinum toxin. Neurology Service, Department of Veterans Affairs Medical Center, Albuquerque, New Mexico.
- Dock M, Ben Ali A, Karras A, Missot B, Garrouste-Orgeas M, Deletie E, Goldstein F and Carlet J (2002). [Treatment of severe botulism with 3,4-diaminopyridine]]. *Presse*

Med **31**:601-2. Summary: **INTRODUCTION:** The specific treatments of botulism with serotherapy and with guanidine are of debatable efficacy. We report a case of nutritional toxin B botulism successfully treated with 3,4-diaminopyridine. **OBSERVATION:** Following a meal, a 69 year-old woman consulted for digestive disorders followed by damage to several cranial pairs, autonomous nervous system and ventilation command, motivating mechanical ventilation on tracheal intubation. Administration of symptomatic treatment with 3,4-diaminopyridine led to progressive improvement, although the diagnosis of toxin B botulism was confirmed. **COMMENTS:** Administration of 3,4-diaminopyridine, the efficacy of which had been suggested by the review of experimental literature, led to rapid and clear improvement, probably due to its potentiating effect on acetylcholine release in the neuromuscular junction. Fondation Hopital Saint-Joseph, Paris.

- Donovan WH, Halter JA, Graves DE, Blight AR, Calvillo O, McCann MT, Sherwood AM, Castillo T, Parsons KC and Strayer JR (2000). Intravenous infusion of 4-AP in chronic spinal cord injured subjects. *Spinal Cord* **38**:7-15. Summary: **STUDY DESIGN:** A prospective double blind cross over trial of intravenous 4-Aminopyridine (4-AP). **OBJECTIVE:** To determine the efficacy of this drug in the treatment of spinal cord injured (SCI) patients for neurologic impairment, pain and spasticity. **SETTING:** The post anesthesia care unit (PACU) of a tertiary care acute hospital. **METHODS:** Twelve paraplegic patients were enrolled in a double blind cross over intravenous trial of 4-Aminopyridine (4-AP). Thirty milligrams of 4-AP or placebo were administered over a 2 h period. Patients were serially examined during and after the infusion clinically for pain, sensorimotor function, hypertonicity and motor control using electromyography (EMG). Samples of blood and cerebrospinal fluid (CSF) were also analyzed at similar intervals. **RESULTS:** Despite penetration of 4-AP into the CSF, no significant differences were noted in the clinical and EMG parameters at the times measured. Individual changes in sensory function were reported by some patients in both the placebo and 4-AP trials, however mean values were not robust. Frequently, patients complained of unpleasant symptoms during the 4-AP infusion. **CONCLUSION:** The intravenous route may not be the best way to administer this drug as no short term benefits were observed. The University of Texas Houston Medical School, USA.

- Greenwood J, Walters CE, Pryce G, Kanuga N, Beraud E, Baker D and Adamson P (2003). Lovastatin inhibits brain endothelial cell Rho-mediated lymphocyte migration and attenuates experimental autoimmune encephalomyelitis. *Faseb J* Summary: Neuroinflammatory diseases, such as multiple sclerosis (MS), result from aberrant leukocyte traffic into the central nervous system (CNS). To breach the specialized blood-brain barrier, activated leukocytes interact with CNS endothelial cells (EC) and activate a CD54-mediated signaling pathway controlling the Rho GTPase. To function correctly Rho requires posttranslational prenylation, and this can be inhibited by depleting the supply of isoprenoids through inhibition of the cholesterol synthesis pathway with 3-hydroxy-3-methylglutaryl CoA reductase (HMG-CoA reductase) inhibitors (statins). Here we show that treatment of brain EC in vitro with lovastatin inhibits Rho-mediated transendothelial T cell migration. This effect can be reversed by supplementation with mevalonolactone, the downstream product of HMG-CoA reductase, or by ectopic expression of myristoylated Rho, which remains active in the absence of prenylation. In

a relapsing-remitting mouse model of MS, lovastatin treatment inhibited leukocyte migration into the CNS and significantly attenuated the development of both acute and relapsing clinical disease. These studies demonstrate that the indirect pharmacological inhibition of Rho proteins in brain EC by statins can inhibit a key stage in the pathogenesis of neuroinflammation, namely leukocyte migration across the blood-brain barrier. These studies demonstrate a novel effect of statins in modulating the immune response in neuroinflammatory diseases and may provide additional rationale for their use in the treatment of MS.

- Halter JA, Blight AR, Donovan WH and Calvillo O (2000). Intrathecal administration of 4-aminopyridine in chronic spinal injured patients. *Spinal Cord* **38**:728-32. Summary: 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 model 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 microg/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 microg/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. Department of Physical Medicine and Rehabilitation, Baylor College of Medicine, Houston, Texas, USA.
- Jost WH, Mielke U, Forrett-Kaminsky MC and Schimrigk K (1992). [Long-term treatment of Lambert-Eaton syndrome by 3, 4 diaminopyridine]. *Rev Neurol (Paris)* **148**:776-9. Summary: A patient with a 5 year history of slow-progressive Lambert-Eaton Myasthenic Syndrome (LEMS) was treated for a period of 12 months with 3,4-diaminopyridine (3,4-DAP). The therapy led to an objective increase in muscle power. During the treatment period, there was no increase in muscle weakness, but attempts at withdrawal of the drug confirmed a progression. The mouth dryness disappeared and autonomic regulation disturbances were improved. All of the laboratory parameters remained unchanged. A neoplasia was excluded by extensive endoscopic and radiological investigations. Side-effects included initial perioral paresthesia and, later, paresthesia down the skin and along the ulnar edge of the forearm. 3,4-DAP seems to be an effective and acceptable long-term symptomatic therapy in LEMS. *Neurologische*

Klinik der Universität des Saarlandes, Homburg/Saar, R.F.A.

- Kanzato N, Motomura M, Suehara M and Arimura K (1999). Lambert-Eaton myasthenic syndrome with ophthalmoparesis and pseudoblepharospasm. *Muscle Nerve* **22**:1727-30. Summary: We report a patient initially diagnosed as having ocular myasthenia gravis who showed progressive ophthalmoparesis and pseudoblepharospasm together with positive acetylcholine receptor antibodies. Repeated evaluation with high-frequency repetitive stimulation revealed an incremental response and elevated titers of antibodies against presynaptic calcium channels, confirming Lambert-Eaton myasthenic syndrome. Systemic evaluation revealed no malignant neoplasm but revealed euthyroid Hashimoto's disease. Immunomodulative therapy including plasma exchange and administration of an immunosuppressant (azathioprine) combined with a potassium-channel blocker (3,4-diaminopyridine) reduced the ocular abnormalities. We conclude that the ocular manifestations in this patient were probably caused by Lambert-Eaton myasthenic syndrome. Department of Neurology, National Okinawa Hospital, Ganeko 3-20-14, Ginowan-shi, Okinawa 901-2214, Japan.

- Lemeignan M, Millart H, Lamiable D, Molgo J and Lechat P (1984). Evaluation of 4-aminopyridine and 3,4-diaminopyridine penetrability into cerebrospinal fluid in anesthetized rats. *Brain Res* **304**:166-9. Summary: 4-aminopyridine (4-AP) and 3,4-diaminopyridine (3,4-DAP) when injected intracisternally to anesthetized rats induced qualitatively similar central nervous system stimulant and convulsant effects at equimolar concentrations. Overall penetrability into cerebrospinal fluid of 4-AP is significantly higher than that of 3,4-DAP after single i.v. administration as evaluated by a high-performance liquid chromatographic determination. The present results can account for the lower central nervous system toxicity of 3,4-DAP when compared to 4-AP previously described after systemic administration.

- Lundh H, Nilsson O, Rosen I and Johansson S (1993). Practical aspects of 3,4-diaminopyridine treatment of the Lambert-Eaton myasthenic syndrome. *Acta Neurol Scand* **88**:136-40. Summary: 3,4-Diaminopyridine (3,4-DAP) given alone or combined with pyridostigmine is the recommended basic therapy in the Lambert-Eaton myasthenic syndrome (LEMS). We present and exemplify our routine test protocol for monitoring drug introduction and treatment regimen of cholinergic drugs in LEMS. The individual drug responses vary and no recommended standard doses exist. Routine electrophysiological repetitive nerve stimulation studies recording amplitude of initial compound muscle action potential (CMAP) in thenar muscles correlate excellently with clinical myasthenic muscle power tests in clinically affected muscle groups. Therefore repetitive clinical muscle power tests, that often are complicated by painful myalgia and activation potentiation, can be replaced by recordings of CMAP in the introduction and clinical follow up of cholinergic drug treatment in LEMS. Also, adverse effects and other treatment problems from the experience of continuous treatment of 19 LEMS patients with 3,4-DAP for up to 10 years are presented. Department of Neurology, Halmstad Hospital, Stockholm, Sweden.

- Lundh H, Nilsson O and Rosen I (1984). Treatment of Lambert-Eaton syndrome: 3,4-

diaminopyridine and pyridostigmine. *Neurology* **34**:1324-30. Summary: We used a new drug, 3,4-diaminopyridine, to treat five patients with the Lambert-Eaton syndrome, one with a carcinoma and four cryptogenic. The effects of intravenous, oral, and rectal administration were evaluated clinically and electrophysiologically after single doses and during continuous treatment for up to 21 months. 3,4-Diaminopyridine effectively ameliorated the neuromuscular and autonomic nervous system disorders without severe side effects. Anticholinesterase drugs strongly potentiated the benefit of 3,4-diaminopyridine.

- Maddison P, Newsom-Davis J and Mills KR (1998). Effect of 3,4-diaminopyridine on the time course of decay of compound muscle action potential augmentation in the Lambert-Eaton myasthenic syndrome. *Muscle Nerve* **21**:1196-8. Summary: 3,4-Diaminopyridine (3,4-DAP) is known to be beneficial in the symptomatic treatment of the Lambert-Eaton myasthenic syndrome (LEMS). The effects of 3,4-DAP on the decay of postexercise augmentation were observed in 6 patients with LEMS. After 10 s maximal voluntary contraction, the amplitude of the compound muscle action potential (CMAP) recorded from abductor digiti minimi decayed exponentially after an initial rise. The rate of decay in CMAP amplitude was increased after treatment with 3,4-DAP, suggesting that this drug has an effect on the efflux of calcium ions from the presynaptic nerve terminal. University Department of Clinical Neurology, Radcliffe Infirmary, Oxford, United Kingdom.

- Molgo J and Guglielmi JM (1996). 3,4-Diaminopyridine, an orphan drug, in the symptomatic treatment of Lambert-Eaton myasthenic syndrome. *Pflugers Arch* **431**:R295-6. Summary: The Lambert-Eaton myasthenic syndrome (LEMS) is a rare autoimmune disease of peripheral cholinergic transmission that results in muscle weakness and autonomic dysfunction, due to impaired acetylcholine release. A review of available clinical information indicates that 3,4-diaminopyridine (3,4-DAP) used either alone or in conjunction with other therapies was effective in treating the motor and the autonomic deficits in patients with primary and paraneoplastic LEMS of varying degrees of severity. A survey of the medical literature indicates that about 150 patients have been treated worldwide with 3,4-DAP. The general view is that 3,4-DAP is well tolerated in short- or long-term treatments, with only mild side effects. 3,4-DAP is an orphan drug approved for clinical use in many European countries that lacks adoptive parents because its exploitation is not profitable. Laboratoire de Neurobiologie Cellulaire et Moléculaire, C.N.R.S., Gif-sur-Yvette, France.

- Newsom-Davis J (2001). Lambert-Eaton Myasthenic Syndrome. **3**:127-131. Summary: Weakness and autonomic dysfunction in Lambert-Eaton myasthenic syndrome (LEMS) can be partially or fully controlled by 3,4-Diaminopyridine. Intravenous immunoglobulin or plasma exchange (PE) plasmapheresis provides short-term improvement in severely affected patients. In those at risk from paraneoplastic LEMS (cigarette smokers), an intensive search for lung cancer should be undertaken, and specific tumor therapy instituted that likely will improve the neurologic deficit. Prednisolone (1.5 mg per kg of body weight administered on alternate days, maximum dosage is 100 mg) is indicated in those with paraneoplastic or nonparaneoplastic LEMS who fail to respond sufficiently to symptomatic treatment. The addition of azathioprine

or cyclosporine is indicated as corticosteroid sparing medications in nonparaneoplastic LEMS. When remission or optimal improvement is judged to be present, prednisolone should be tapered to the minimum dose that effectively controls symptoms. If full withdrawal is achieved, azathioprine dose reduction is similarly initiated. In nonparaneoplastic LEMS patients failing to respond to azathioprine after 1 to 2 years of therapy, physicians should consider substituting cyclosporine. Department of Clinical Neurology, University of Oxford, Radcliffe Infirmary, Oxford, OX2 6HE, UK.

- Oishi K, Oya Y, Yamamoto T, Shigeto H, Ogawa M and Kawai M (2001). [Quantitative evaluation of the effect of 3,4-diaminopyridine in a patient with Lambert-Eaton myasthenic syndrome using dynamic dynamometry]. *Rinsho Shinkeigaku* **41**:515-8. Summary: We reported a 72-year-old woman with Lambert-Eaton myasthenic syndrome. The chief complaint was weakness and atrophy of the thigh muscles, which prevented her from climbing stairs even with a handrail. Sensory and autonomic function was normal without amblygeusia. There was no malignancy found, and her serum anti-V/Q type voltage-gated calcium channel antibody was negative. Administration of 3,4-diaminopyridine (DAP), known to accelerate acetylcholine release, was very effective and she became able to climb stairs without a handrail. For evaluation of the therapeutic effect of DAP, the initial compound muscle action potential (ICMAP) on evoked electromyogram has been recommended because it provides highly sensitive and reproducible results. Unfortunately this method is usually applied to several particular distal muscles for technical reasons. In the present case, evaluation of the quadriceps femoris muscle was most important because it was most responsible for her disability. We attempted to measure the angular velocity and the angular acceleration on knee extension movement using dynamic dynamometry. The angular velocity improved from 124 to 162 deg/sec and the angular acceleration from 220 to 390 deg/sec². The results were more sensitive and more relevant to her demonstrable ADL improvement than grasping power increase and ICMAP improvement recorded at the distal muscles. Division of Endocrinology/Metabolism, Neurology and Hematology/Oncology, Department of Clinical Molecular Medicine, Kobe University School of Medicine, Kobe.

- Palace J, Wiles CM and Newsom-Davis J (1991). 3,4-Diaminopyridine in the treatment of congenital (hereditary) myasthenia. *J Neurol Neurosurg Psychiatry* **54**:1069-72. Summary: Congenital or hereditary myasthenia describes a heterogeneous group of disorders in which the immune system is not implicated. Treatment has previously depended on anticholinesterase medication. The effectiveness of 3,4-diaminopyridine (3,4-DAP), a preparation that enhances acetylcholine release from motor nerve terminals, has been evaluated using a series of standardised strength measures. Sixteen patients (aged seven to 47 years) were studied in an open prospective trial, and four of them in a double blind crossover trial; existing anticholinesterase medication was continued. For the group as a whole, there was a highly significant increase in muscle strength (p less than 0.001; $n = 16$). In individual paired comparisons, 13 out of 16 showed significant improvement in the open trial and four out of four in the blind crossover trial. In conclusion, 3,4-DAP, either alone or combined with anticholinesterase medication, may be a useful additional treatment in congenital myasthenia. Department of Neurology, Radcliffe Infirmary, University of Oxford, UK.

- Petty MA and Lo EH (2002). Junctional complexes of the blood-brain barrier: permeability changes in neuroinflammation. *Prog Neurobiol* **68**:311-23. Summary: A wide range of central nervous system (CNS) disorders include neuroinflammatory events that perturb blood-brain barrier (BBB) integrity. Mechanisms by which the BBB responds to physiological and pathological stimuli involve signaling systems in the tight and adherens junctions of the cerebral endothelium. In this review, we examine the molecular composition and regulatory mediators that control BBB permeability and assess how these mediators may be dysregulated in stroke, multiple sclerosis, brain tumors, and meningioencephalitis. An understanding of these molecular substrates in BBB regulation may lead to new approaches for enhancing CNS drug delivery and ameliorating brain edema after injury and inflammation. CNS Pharmacology, Aventis Pharmaceuticals Inc., Route 202-206, P.O. Box 6800, 08807, Bridgewater, NJ, USA

- Pickett TA and Enns R (1996). Atypical presentation of 4-aminopyridine overdose. *Ann Emerg Med* **27**:382-5. Summary: 4-Aminopyridine (4-AP) is an investigational drug for the treatment of neurologic disorders including multiple sclerosis (MS). Until recently, relatively little was known about 4-AP toxicity in overdose; the only recorded cases involved neurologic symptoms ranging from mild parasthesias to tonic-clonic seizures. We report a case of accidental 4-AP overdose that resulted in continuous, dystonic, choreoathetoid-type movements that responded to treatment with standard anticonvulsant dosages of benzodiazepines. Department of Emergency Medicine, Vancouver Hospital and Health Sciences Centre, Vancouver, British Columbia, Canada.

- Polman CH, Bertelsmann FW, de Waal R, van Diemen HA, Uitdehaag BM, van Loenen AC and Koetsier JC (1994). 4-Aminopyridine is superior to 3,4-diaminopyridine in the treatment of patients with multiple sclerosis. *Arch Neurol* **51**:1136-9. Summary: 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. Department of Neurology, Free University Hospital, Amsterdam, The Netherlands.

- Polman CH, Bertelsmann FW, van Loenen AC and Koetsier JC (1994). 4-aminopyridine in the treatment of patients with multiple sclerosis. Long-term efficacy and safety. *Arch Neurol* **51**:292-6. Summary: OBJECTIVE: To study the long-term efficacy and safety of 4-aminopyridine in patients with multiple sclerosis. DESIGN: Case series, follow-up varying from 6 to 32 months. SETTING: University referral center. PATIENTS: Thirty-one patients with definite MS, 23 of them being exposed to long-term administration (6 to 32 months) of 4-aminopyridine, since they showed a favorable initial response to the drug. INTERVENTIONS: Long-term oral treatment with 4-aminopyridine in daily doses of up to 0.5 mg/kg of body weight. MAIN OUTCOME MEASURES: Neurologic functions and symptoms as reported by the patients; side effects. RESULTS: Twenty of 23 patients who showed a favorable initial response benefited from long-term administration. Ambulation and fatigue (each in 13 patients) and visual function (in five patients) were most frequently reported to be improved. Three major side effects did occur during a follow-up of 406 patient months: a generalized epileptic seizure in two patients and hepatitis in one. CONCLUSIONS: Although a substantial proportion of patients with multiple sclerosis seem to benefit from long-term administration of 4-aminopyridine, additional studies are needed to clarify the exact value of the drug. Department of Neurology, Free University Hospital, Amsterdam, The Netherlands.

- Potter PJ, Hayes KC, Hsieh JT, Delaney GA and Segal JL (1998). Sustained improvements in neurological function in spinal cord injured patients treated with oral 4-aminopyridine: three cases. *Spinal Cord* **36**:147-55. Summary: Preclinical trials of intravenously administered 4-Aminopyridine (4-AP) have demonstrated transient improvements in neurological function in patients with longstanding spinal cord injury (SCI). The present report describes three patients with SCI who responded favourably in preclinical trials and who were subsequently administered oral (capsule) 4-AP (10 mg b.i.d. or t.i.d.) over a 4 month interval. The three patients (two male: 1 female) all had incomplete tetraplegia (ASIA levels C and D) with the neurological level of the lesion between C5-C7. Following the administration of 4-AP the patients demonstrated marked and sustained reductions in upper (n = 1) or lower extremity (n = 2) spasticity. Other clinical benefits of 4-AP were reduced pain (n = 1), restored muscle strength (n = 3), improved sensation (n = 2), voluntary control of bowel function (n = 1), and sustained penile tumescence (n = 2). The patients exhibited improved hand function (n = 1), enhanced mobility in transfers and gait (n = 2), with improved energy and endurance. Only trivial side effects (transient light-headedness) were observed. In one case, the enhanced neurological function allowed the patient to stand with support for the first time post injury (16 years). The time course of therapeutic response to the initial dose matched the pharmacokinetic elimination profile derived from serum and urine analysis. There was no evidence of renal or hepatic toxicity with prolonged use. These results indicate a therapeutic benefit of oral 4-Aminopyridine in the management of various neurological deficits in a select group of SCI patients. Department of Physical Medicine & Rehabilitation, Parkwood Hospital, London, Ontario, Canada.

- Potter PJ, Hayes KC, Segal JL, Hsieh JT, Brunnemann SR, Delaney GA, Tierney DS and Mason D (1998). Randomized double-blind crossover trial of fampridine-SR

(sustained release 4-aminopyridine) in patients with incomplete spinal cord injury. *J Neurotrauma* **15**:837-49. Summary: A randomized double-blind dose-titration crossover trial of the safety and efficacy of oral fampridine-SR (sustained release 4-aminopyridine) was conducted on spinal cord injured (SCI) patients at two centers. Twenty-six patients (n = 26) with incomplete lesions completed the trial. These patients all had chronic (>2 years) and stable neurological deficits. They received fampridine-SR 12.5 and 17.5 mg b.i.d. over a 2-week treatment period, followed by a 1-week washout and 2 weeks of placebo, or vice versa. Patients reported significant benefit of fampridine-SR over placebo on patient satisfaction (McNemar's test, $p_2 < 0.05$) and quality of life scores ($p_2 < 0.01$). Sensory scores ($p_1 < 0.01$), including both pin prick ($p_1 = 0.059$) and light touch ($p_1 = 0.058$), and motor scores (adjusted to reflect only paretic segments) ($p_1 < 0.01$) all yielded evidence of benefit of fampridine-SR over placebo. The Ashworth scale of spasticity was significantly ($p_2 < 0.05$) reduced when patients received fampridine-SR. There were no statistically significant benefits of the drug on measures of pain or bowel, bladder and sexual function, or functional independence. Side effects of lightheadedness and nausea were transient and trivial relative to efficacy, and approximately 30% of patients reported a wish to continue to use fampridine-SR. The clinical benefits most likely derive from the K⁺ channel blocking action of the drug. Potassium channel blockade enhances axonal conduction across demyelinated internodes and enhances neuroneuronal and neuromuscular transmission in preserved axons. These results provide the first evidence of therapeutic benefit of fampridine-SR in SCI patients. Department of Physical Medicine and Rehabilitation, Parkwood Hospital, University of Western Ontario, London, Canada.

- Pratt K, Toombs JP, Widmer WR and Borgens RB (1995). Plasma and cerebrospinal fluid concentrations of 4-aminopyridine following intravenous injection and metered intrathecal delivery in canines. *J Neurotrauma* **12**:23-39. Summary: Potassium channel blockade by 4-aminopyridine (4-AP) has been shown to initiate modest levels of functional recovery in spinal-injured dogs and people following intravenous administration; however, the relevant central nervous system (CNS) concentration mediating these effects is not known. We have determined the concentrations of 4-aminopyridine in plasma and cerebrospinal fluid following intravenous administration (0.5 mg/kg) in large (> 22 kg) dogs, using liquid column chromatography. Plasma levels are initially high (> 1 microgram/mL) and fall rapidly to levels less than 100 ng/mL by about 2 h postinjection. A characteristic secondary peak in plasma 4-AP is observed at about 1 h postinjection. Corresponding concentrations of 4-AP in CSF were relatively stable for nearly 2 h, never exceeding (as a mean) 50 ng/mL within the first 2 h postinjection. We suggest behavioral recovery in clinical cases of spinal cord injury in both dogs and humans is mediated by such low (< 50 ng/mL) concentrations of 4-AP bathing the lesion. Since the adverse side effects that accompany IV administration of the drug limit its potential clinical usefulness, we have evaluated the feasibility of an alternate route of administration, continuous metered delivery of 4-AP into the spinal cord's subarachnoid space. This is accomplished by using a surgically implantable pump and delivery catheter. The pump itself can be interrogated, and is fully programmable, by noninvasive telemetry. Intrathecal delivery rates of between 1 and 60 micrograms of 4-AP per hour never produced detectable levels of the drug in plasma or cervically sampled CSF in dogs independent of the amount or duration of infusion (hours to days).

The levels of 4-AP in lumbar samples of CSF near the lumbar delivery site suggest a very steep gradient of the drug, with local concentrations easily reaching 1 microgram/mL or higher (10- to 20-fold higher than can be safely produced by IV administration). The most frequent adverse reaction to intrathecal 4-AP delivery was a mild hindlimb tremor, fully reversible following reduction in the rate of drug delivery or termination of delivery. This route of drug administration relative to clinical spinal cord injury is discussed. Division of Neurosurgery, Indiana University School of Medicine, Indianapolis, USA.

- Proescholdt MA, Jacobson S, Tresser N, Oldfield EH and Merrill MJ (2002). Vascular endothelial growth factor is expressed in multiple sclerosis plaques and can induce inflammatory lesions in experimental allergic encephalomyelitis rats. *J Neuropathol Exp Neurol* **61**:914-25. Summary: The active lesions in multiple sclerosis (MS) are characterized by blood-brain-barrier (BBB) breakdown, upregulation of adhesion molecules on capillary endothelial cells, and perivascular inflammation, suggesting that altered vessel permeability and activated endothelial cells are involved in the pathogenesis of the disease. Vascular endothelial growth factor (VEGF) mediates multiple aspects of blood vessel physiology, including regulation of growth, permeability, and inflammation. To investigate a possible relationship between VEGF expression and CNS autoimmune disease, we examined VEGF expression in MS plaques compared to normal white matter by immunohistochemistry and in situ hybridization. VEGF expression was consistently upregulated in both acute and chronic MS plaques. We also examined VEGF expression during the course of experimental allergic encephalomyelitis (EAE) in rats. VEGF-positive cells with astrocytic morphology increased in the spinal cord during the development of EAE and were found in association with inflammatory cells. Furthermore, intracerebral infusion of VEGF in animals previously immunized with myelin basic protein induced an inflammatory response in the brain, whereas infusion of vehicle, or infusion of VEGF in naive animals, did not. These results suggest that overexpression of VEGF may exacerbate the inflammatory response in autoimmune diseases of the CNS by inducing focal BBB breakdown and migration of inflammatory cells into the lesions. Surgical Neurology Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland 20892-1414, USA.

- Rosenberg GA (2002). Matrix metalloproteinases and neuroinflammation in multiple sclerosis. *Neuroscientist* **8**:586-95. Summary: Matrix metalloproteinases (MMPs) are extracellular matrix remodeling neutral proteases that are important in normal development, angiogenesis, wound repair, and a wide range of pathological processes. Growing evidence supports a key role of the MMPs in many neuroinflammatory conditions, including meningitis, encephalitis, brain tumors, cerebral ischemia, Guillain-Barre, and multiple sclerosis (MS). The MMPs attack the basal lamina macromolecules that line the blood vessels, opening the blood-brain barrier (BBB). They contribute to the remodeling of the blood vessels that causes hyalinosis and gliosis, and they attack myelin. During the acute inflammatory phase of MS, they are involved in the injury to the blood vessels and may be important in the disruption of the myelin sheath and axons. Normally under tight regulation, excessive proteolytic activity is detected in the blood and cerebrospinal fluid in patients with acute MS. Because they are induced in

immunologic and nonimmunologic forms of demyelination, they act as a final common pathway to exert a "bystander" effect. Agents that block the action of the MMPs have been shown to reduce the damage to the BBB and lead to symptomatic improvement in several animal models of neuroinflammatory diseases, including experimental allergic encephalomyelitis. Such agents may eventually be useful in the control of excessive proteolysis that contributes to the pathology of MS and other neuroinflammatory conditions. Department of Neurology, University of New Mexico Health Sciences Center, Albuquerque, New Mexico 87131, USA. grosenberg@salud.unm.edu

- Russell JW, Windebank AJ and Harper CM, Jr. (1995). Treatment of stable chronic demyelinating polyneuropathy with 3,4-diaminopyridine. *Mayo Clin Proc* **70**:532-9. Summary: OBJECTIVE: To determine whether 3,4-diaminopyridine (3,4-DAP) would improve clinical or electrophysiologic function in patients with stable chronic demyelinating polyneuropathy. DESIGN: We conducted a prospective, randomized, placebo-controlled, blinded, crossover study of 3,4-DAP in 34 patients with demyelinating polyneuropathy. MATERIAL AND METHODS: Of the 17 men and 17 women, who were 21 to 80 years of age, 27 had hereditary motor and sensory neuropathy type I and 7 had acquired demyelinating polyneuropathy. Treatment consisted of stepped doses of 3,4-DAP (increasing to 20 mg four times daily) or placebo for 4 days. Pretreatment and posttreatment determination of the Neurologic Disability Score (NDS); isometric muscle strength testing; median, ulnar, and peroneal nerve conduction studies; and measurement of serum 3,4-DAP were performed. Quantitative computer-assisted sensory examinations were done in five patients. RESULTS: The results for the final day of treatment with 3,4-DAP or placebo and the differences between pretreatment and posttreatment findings for total NDS, sensory NDS, isometric muscle strength testing, compound muscle action potential amplitude, sensory nerve action potential amplitude, motor and sensory conduction velocities, and vibration and cold detection thresholds did not vary significantly. A small improvement of 4 points in the motor NDS ($P < 0.05$) was found. Five patients with electrophysiologic conduction block had no significant reduction in the degree of block. CONCLUSION: Because no improvement was noted in most measurements of neurologic function, despite use of high doses of drug, 3,4-DAP is unlikely to be beneficial in the treatment of stable chronic demyelinating polyneuropathy. Department of Neurology, Mayo Clinic Rochester, Minnesota 55905, USA.

- Sanders DB, Massey JM, Sanders LL and Edwards LJ (2000). A randomized trial of 3,4-diaminopyridine in Lambert-Eaton myasthenic syndrome. *Neurology* **54**:603-7. Summary: OBJECTIVES: The authors report the results of a prospective, placebo-controlled, randomized study to evaluate the effectiveness of 3,4-diaminopyridine (DAP) in patients with Lambert-Eaton myasthenic syndrome (LEMS) and to determine the acute and long-term side effects of DAP. METHODS: Twenty-six patients with LEMS completed a two-arm parallel treatment protocol in which DAP, 20 mg three times daily, or placebo was given blindly for 6 days, and a quantitative examination of muscle strength (the quantitative myasthenia gravis [QMG] score) was used as the primary measure of efficacy. After the blinded study, patients were given open-label DAP and monitored for side effects as long as there was symptomatic improvement. RESULTS: Twelve patients took DAP, and 14 took placebo. There was no difference in

the age of LEMS onset, gender distribution, incidence of lung cancer, or baseline muscle strength between the patients who were randomly assigned to receive placebo and those randomly assigned to DAP. Statistical analysis using the Wilcoxon's rank sum test demonstrated that patients who received DAP had a significantly greater improvement in the QMG score and in the summated amplitude of compound muscle action potentials recorded from three sentinel limb muscles. All but one LEMS patient had significant symptomatic improvement from subsequent open-label DAP. Side effects of DAP were negligible, consisting of perioral and digital paresthesia. Laboratory measurements demonstrated no evidence of toxicity affecting liver, renal, hematologic, endocrinologic, encephalographic, or electrocardiologic function acutely or after 6 months of open-label DAP. CONCLUSIONS: This study corroborates previous studies and many years of clinical experience showing that DAP is an effective and safe treatment for LEMS. Department of Medicine, Duke University Medical Center, Durham, NC 27710, USA.

- Satoh K, Motomura M, Suzu H, Nakao Y, Fujimoto T, Fukuda T, Nakane S, Nakamura T and Eguchi K (2001). Neurogenic bladder in Lambert-Eaton myasthenic syndrome and its response to 3,4-diaminopyridine. *J Neurol Sci* **183**:1-4. Summary: Autonomic dysfunction, as well as neuromuscular involvement, is a common manifestation of Lambert-Eaton myasthenic syndrome (LEMS). Dry mouth and impotence have been described as typical features of autonomic dysfunction, but neurogenic bladder is infrequent or subclinical in LEMS. We report a patient with neurogenic bladder secondary to LEMS whose condition responded to 3,4-diaminopyridine (3,4-DAP). In this patient's serum, results of repeated measurement with P/Q-type VGCC antibodies proved positive, but not with N-type VGCC and synaptotagmin antibodies. A review of the literature turned up a few patients with voiding dysfunction related to LEMS, but no urodynamic studies were done on these patients. Ours is the first case in which 3,4-DAP was efficacious in treating LEMS and neurogenic bladder. Responses of 3,4-DAP in urodynamic studies suggest that in this LEMS patient neurogenic bladder was caused by defective neurotransmission both in the autonomic detrusor and skeletal abdominal muscles. First Department of Internal Medicine, Nagasaki University School of Medicine, 1-7-1 Sakamoto, 852-8501, Nagasaki, Japan.

- Sheean GL, Murray NM, Rothwell JC, Miller DH and Thompson AJ (1998). An open-labelled clinical and electrophysiological study of 3,4 diaminopyridine in the treatment of fatigue in multiple sclerosis. *Brain* **121 (Pt 5)**:967-75. Summary: We studied the electrophysiological parameters of motor performance in eight patients with multiple sclerosis and troublesome fatigue, before and after treatment with 3,4-diaminopyridine. Symptomatic fatigue was evaluated by the Krupp Fatigue Severity Score and motor performance of adductor pollicis by transcranial magnetic stimulation, rapid voluntary movements and a fatiguing exercise test of a sustained 45-s isometric contraction. The motor tests revealed baseline abnormal motor function and substantial central fatigue. After a 3-week course of 3,4-diaminopyridine (25-60 mg/day), six out of the eight patients reported substantial improvement in fatigue and the group showed slightly less fatigue on the exercise test. Other electrophysiological tests of motor function were unchanged. The findings suggest that 3,4-diaminopyridine may play a role in the symptomatic treatment of fatigue in multiple sclerosis. However, the mechanism behind

such a benefit in fatigue remains unclear and the discrepancy between subjective and more objective responses underlines the probable multifactorial nature of the pathogenesis of this symptom in multiple sclerosis. Department of Clinical Neurophysiology, National Hospital for Neurology and Neurosurgery, London, UK.

- Smeets JW and Kunst MW (1995). [Severe poisoning by 4-aminopyridine in a body builder]. *Ned Tijdschr Geneeskd* **139**:2667-9. Summary: A 22-year-old man was admitted to hospital with severe, accidental intoxication with 4-aminopyridine, a medicine which increases the acetylcholine concentration in the synapses and has a limited application in the treatment of some neurological diseases. The patient acted on the assumption of body-building capacities of this 'amino'. Apart from the previously documented symptoms of intoxication such as an epileptic attack and confusion, he showed cardiac arrhythmias, conduction disorders and severe hypertension. The serum concentration of 4-aminopyridine was 335 mg/l, while the therapeutic level is 25-75 mg/l. Rode Kruis Ziekenhuis, afd. Interne Geneeskunde, Beverwijk.

- Smith AG and Wald J (1996). Acute ventilatory failure in Lambert-Eaton myasthenic syndrome and its response to 3,4-diaminopyridine. *Neurology* **46**:1143-5. Summary: Respiratory failure is a common manifestation of myasthenia gravis but is infrequent in Lambert-Eaton myasthenic syndrome (LEMS), where it is often related to the use of paralytic agents or intercurrent pulmonary pathology. Therapies that are effective acutely in myasthenia gravis are usually of minimal benefit in LEMS. We describe a patient with respiratory failure secondary to LEMS who responded to 3,4-diaminopyridine and review the 12 previously reported cases of ventilatory failure in LEMS. Department of Neurology, University of Michigan Medical Center, Ann Arbor 48109, USA.

- Solari A, Uitdehaag B, Giuliani G, Pucci E and Taus C (2001). Aminopyridines for symptomatic treatment in multiple sclerosis. *Cochrane Database Syst Rev* CDO01330. Summary: **BACKGROUND:** Because of their ability to increase nerve conduction in demyelinated nerve fibers, potassium channel blockers 4-aminopyridine (AP) and 3,4-diaminopyridine (DAP) have been proposed as a symptomatic therapy for people with multiple sclerosis (MS). **OBJECTIVES:** To determine the efficacy and safety of aminopyridines in improving neurological deficits in people with MS. **SEARCH STRATEGY:** Computerised general (MEDLINE, EMBASE) and specialised databases (Cochrane MS Group's trials register, CCTR). Hand search of bibliographic references from retrieved studies and recent MS symposia reports. Contact with principal investigators of known studies. **SELECTION CRITERIA:** Trials were included if they fulfilled all following criteria: randomised controlled trials (RCTs); adults with MS, out of exacerbation; AP or DAP treatment versus placebo; clinical endpoints. **DATA COLLECTION AND ANALYSIS:** We identified 26 potentially pertinent studies. Three reviewers independently extracted data and assessed trial quality from the 16 studies available as full papers. **MAIN RESULTS:** Five studies (six publications) and 144 participants were considered in this review. Two more abstracts are awaiting assessment. All five studies were single-centre, double-blind, crossover trials. Four studies assessed the efficacy of AP versus placebo, one compared DAP with active placebo. The duration of treatment ranged from hours to three months. The median

quality score of the studies was 3 (range 2-5). The heterogeneity of outcome assessment and the absence of information on individual study periods, allowed quantitative pooling of results for few categorical variables. Of the 144 treated patients, there were six major side effects: one acute encephalopathy, three episodes of confusion, and two seizures. Manual muscle testing was assessed in three studies (54 patients), with 29 patients (54%) improving in at least one muscular district during study treatment versus four patients (7%) during placebo (odds ratio [OR] 14.5, 95% confidence interval [CI] 4.7-43.7). Ambulation was assessed in three studies (54 patients): 9 patients (17%) improved during study treatment versus none during placebo ($p < 0.001$). An improvement in EDSS score was found in 13 of the 144 participants during study treatment (9%) versus none during placebo ($p < 0.001$). No improvement in neuropsychological tests was found in the two trials that evaluated cognitive function. Finally, 47 of 136 people with MS (35%) felt improved when receiving the study drug, against 7(5%) on placebo (OR 9.7, 95% CI 4.3-22.0). REVIEWER'S CONCLUSIONS: Based on currently available information, no unbiased statement can be made about the safety or efficacy of aminopyridines for treating MS symptoms. Furthermore, we could not obtain any data on three unpublished RCTs involving more than 300 participants. We conclude that publication bias remains a pervasive problem in this area, and that until the results of these unpublished studies are available to the scientific community, no confident estimate of effectiveness of aminopyridines in the management of MS symptoms is possible. Laboratory of Epidemiology, National Neurological Institute Carlo Besta, Via Celoria 11, Milan, Italy, 20133. solari@istituto-besta.it

- Spyker DA, Lynch C, Shabanowitz J and Sinn JA (1980). Poisoning with 4-aminopyridine: report of three cases. *Clin Toxicol* **16**:487-97. Summary: Four-aminopyridine is an acutely toxic avicide considered by the manufacturer to be a bird "repellant" because only a small number of birds are acutely poisoned, become disoriented, and emit a distress cry frightening other members of the flock. Four-aminopyridine dramatically enhances transmission at the neuromuscular junction and other synapses, and has been employed clinically in the treatment of prolonged paralysis caused by antibiotics and muscle relaxants, and in the Eaton-Lambert syndrome. In this paper we report the results of an acute poisoning misadventure in three adult males. We review the animal toxicology, summarize the neurophysiological research using 4-AP as a potassium channel blocker, comment on clinical applications, and outline the management of overdose with this agent.

- Tim RW, Massey JM and Sanders DB (2000). Lambert-Eaton myasthenic syndrome: electrodiagnostic findings and response to treatment. *Neurology* **54**:2176-8. Summary: The authors reviewed the incidence of cancer, repetitive nerve stimulation findings, and response to treatment in 73 patients with Lambert-Eaton myasthenic syndrome. Thirty-one patients (42%) had lung cancer, 29 small cell. Doubling of the compound motor action potential amplitude in three tested distal muscles was seen in only 41% of patients. Treatment with 3, 4-diaminopyridine produced moderate to marked self-reported functional improvement in 79% of the 53 treated patients. Duke University Medical Center, Durham, NC 27710, USA. rtim@acpub.duke.edu

- Trevett AJ, Lalloo DG, Nwokolo NC, Naraq S, Kevau IH, Theakston RD and Warrell DA (1995). Failure of 3,4-diaminopyridine and edrophonium to produce significant clinical benefit in neurotoxicity following the bite of Papuan taipan (*Oxyuranus scutellatus canni*). *Trans R Soc Trop Med Hyg* **89**:444-6. Summary: Progressive systemic neurotoxicity is a common feature in patients envenomed following the bite of a Papuan taipan (*Oxyuranus scutellatus canni*). Respiratory paralysis, which commonly results, accounts for considerable morbidity and mortality. Established neurotoxicity does not respond to antivenom. In this study, a combination of clinical and electrophysiological variables was used to assess the effect of edrophonium and 3,4-diaminopyridine in patients with significant neurotoxicity. Both drugs produced minor electrophysiological and clinical changes in envenomed patients. This effect was maximal when the 2 drugs were used in combination, but was insufficient to be of significant clinical benefit. Neither drug can be recommended for use in the management of Papuan taipan bite. Department of Clinical Sciences, University of Papua New Guinea, Port Moresby, Papua New Guinea.

- Tsuchiya N, Sato M, Uesaka Y, Kurose N, Haida M, Nakano J, Tsuchida T, Inoue T and Ito K (1993). Lambert-Eaton myasthenic syndrome associated with Sjogren's syndrome and discoid lupus erythematosus. *Scand J Rheumatol* **22**:302-4. Summary: A 65-year-old woman with facial erythema and hypergammaglobulinemia developed excessive fatigability. A diagnosis of Lambert-Eaton myasthenic syndrome (LEMS) was made from electrophysiological studies. She had symptoms and laboratory data compatible with probable Sjogren's syndrome. Skin biopsy revealed the histological findings of discoid lupus erythematosus. Treatment with 3,4-diaminopyridine resulted in the improvement of fatigability. LEMS should be recognized as a treatable complication of systemic autoimmune diseases. Department of Medicine and Physical Therapy, University of Tokyo, Japan.

- van der Bruggen MA, Huisman HB, Beckerman H, Bertelsmann FW, Polman CH and Lankhorst GJ (2001). Randomized trial of 4-aminopyridine in patients with chronic incomplete spinal cord injury. *J Neurol* **248**:665-71. Summary: OBJECTIVE: To test the efficacy of 4-aminopyridine (4-AP) on functional status, walking speed and vibration perception in patients with chronic, incomplete spinal cord injury. METHODS: Twenty SCI patients were randomized in a trial with a double-blind, crossover design to receive four weeks of orally administered 4-AP, followed by a two-week wash-out period and four weeks of placebo, or vice versa. The total daily dose of 4-AP during the four weeks of treatment was systematically increased to a maximum of 0.5 mg/kg body weight. Evaluation of (side-)effects took place at the beginning, after one week, and at the end of each four-week study period. RESULTS: No significant benefit was found on functional status (COOP-WONCA). A statistically significant treatment effect was found on the vibration perception threshold (VPT) in the left fingers, during the first study period. On average, patients receiving 4-AP treatment responded less favourably (mean increase in VPT of 0.29 (0.31) microm) than patients receiving placebo (mean decrease in VPT of 0.05 (0.35) microm) ($p=0.04$). Neither comfortable nor maximum walking speed altered significantly following 4-AP treatment. CONCLUSIONS: No statistically significant, functional benefit from 4-AP was found for patients in the present study. Furthermore, no support was found for the possibility that an a priori selection of

responsive patients would have yielded more favourable results. Department of Rehabilitation Medicine, University Hospital Vrije Universiteit Amsterdam, The Netherlands. h.beckerman@azvu.nl

- Velez L, Shirazi F, Goto C, Shepherd G and Roth BA (2003). Opisthotonic posturing with neuromuscular irritability attributable to 4-aminopyridine ingestion by a healthy pediatric patient. *Pediatrics* **111**:e82-4. Summary: INTRODUCTION: 4-Aminopyridine (4-AP) is a potassium channel blocker used to increase muscle strength in the treatment of demyelinating diseases such as multiple sclerosis. We describe a case of ingestion by an 8-month-old child that resulted in severe but transient symptoms. CASE REPORT: An 8-month-old boy was found with greenish saliva, and a capsule with green 4-AP powder was missing. On arrival to an emergency department, he was jittery, tachycardic, and tachypneic. Activated charcoal, a cathartic, and midazolam (0.5 mg/kg) were administered before transfer to a tertiary pediatric hospital. On arrival, the infant remained tachycardic and tachypneic. His eyes deviated upward and he was noted to have 3+ deep tendon reflexes bilaterally. He was administered 0.9% normal saline (20 mL/kg) for a wide pulse pressure with low diastolic blood pressure. The patient developed dramatic opisthotonic posturing and vermiform tongue fasciculations. The symptoms responded well to repeated intravenous doses of benzodiazepines. In this case, we used 2 doses of lorazepam (0.05 mg/kg each). During opisthotonic posturing, an electroencephalogram performed in the intensive care unit revealed no evidence of seizure activity. Within 20 hours after admission, the patient became asymptomatic. CONCLUSION: This case is, to our knowledge, the first documented pediatric 4-AP ingestion. Clinical signs and symptoms are described as well as the response to therapy with benzodiazepines. The electroencephalogram performed while the patient was symptomatic was negative for seizures. North Texas Poison Center, Dallas, Texas, USA. larissa.velez@utsouthwestern.edu