

Opisthotonic Posturing With Neuromuscular Irritability Attributable to 4-Aminopyridine Ingestion by a Healthy Pediatric Patient

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ABSTRACT. *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. *Pediatrics* 2003;111:e82–e84. URL: <http://www.pediatrics.org/cgi/content/full/111/1/e82>; *opisthotonus, 4-aminopyridine, 4-AP, toxicology.*

ABBREVIATIONS. 4-AP, 4-aminopyridine; ED, emergency department; IV, intravenous(ly); PICU, pediatric intensive care unit.

In 1924, 4-aminopyridine (4-AP) was first described as an avicide. The drug acts by producing a potassium channel blockade, which results in prolongation of the action potential and increased neuromuscular transmission.^{1–3} Potassium channels affect the rectifying current during repolarization. If the channels are blocked, the action potential is pro-

longed. The net result is increased influx of calcium into the cell. The increased intracellular calcium leads to more neurotransmitter release.

Its first clinical use in humans was described in the early 1980s.⁴ 4-AP is an orphan drug used to treat disorders of neuromuscular transmission and demyelinating diseases like multiple sclerosis, Eaton-Lambert syndrome, and myasthenia gravis.^{5–10} In addition, it has been used in Europe to reverse the neuromuscular blockade produced by nondepolarizing neuromuscular blocking agents.¹¹ The use of 4-AP for calcium channel blocker intoxication has also been explored.^{12–14} Currently, there is limited information available about 4-AP poisoning in humans.

CASE REPORT

A previously healthy 8-month-old white boy presented to an emergency department (ED) 40 minutes after he was found ingesting up to 20 mg of his grandmother's 4-AP. His grandfather found him with green-colored saliva around his mouth, which is the same color as the contents of the 4-AP capsule. This capsule was the only one missing, according to relatives. On arrival to the outside ED, the boy was described as being jittery, tachypneic (respiratory rate 50–60/min), tachycardic (heart rate 170–180/min), diaphoretic, and with eyes rolling backwards. After consultation with the Poison Control Center, the patient was started on intravenous (IV) fluids and was given activated charcoal (1 g/kg) and 0.5 mg/kg (4 mg total) of midazolam IV. Transfer arrangements were made, and he was transported to a pediatric tertiary care facility.

At the receiving hospital's ED the vital signs were as follows: blood pressure 105/24 mm Hg, heart rate 127–150/min, respiratory rate 50–60/min, temperature 36.9°C (tympanic), and pulse oximetry 89% at room air. On physical examination he was awake but did not respond appropriately to external stimuli. There was no evidence of trauma. He was irritated and crying, with increased muscle tone and generalized 3+ deep tendon reflexes. He also had a continuous upward gaze and vertical nystagmus. His lungs were clear to auscultation, and the heart examination was normal. The abdomen was soft with normal bowel sounds.

The patient received a 20 mL/kg bolus of normal saline because of the wide pulse pressure and 0.05 mg/kg of lorazepam IV for the agitation. He progressed to opisthotonic posturing and vermiform fasciculation of the tongue. After this deterioration, he was given a second dose of lorazepam (0.05 mg/kg) IV and a second fluid bolus. His motor irritability improved after the administration of benzodiazepines, with almost complete resolution of the opisthotonic posturing previously described. The deep tendon reflexes remained 3+. The patient was admitted to the pediatric intensive care unit (PICU).

Laboratories were drawn in the ED. Arterial blood gas analysis showed a pH of 7.35; pCO₂, 40 mm Hg; pO₂, 117 mm Hg; and HCO₂, 22. The electrocardiogram showed sinus tachycardia with a rate of 118/min. There were no prolonged QRS complex, ST segment, or T wave changes. The complete blood count and chemistries were as follows: hemoglobin, 12.2 g/dL; hematocrit, 36.2%; white blood cells, 14.3 × 10⁵/mm³; platelets, 403 × 10³/mm³; sodium, 140

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mEq/L; potassium, 3.4 mEq/L; chloride, 108 mEq/L; bicarbonate, 22 mEq/L; blood urea nitrogen, 12 mg/dL; creatinine, 0.4 mg/dL; calcium, 9.7 mg/dL; magnesium, 2.0 mEq/L; and phosphate, 4.9 mg/dL. Liver function tests were aspartate aminotransferase, 53 IU/L; alanine aminotransferase, 40 IU/L; creatinine kinase, 779 IU/L; and alkaline phosphatase, 231 IU/L. A qualitative urine toxicology screen (AxSYM, Abbott Laboratories, Abbott Park, IL) was performed and found to be negative for amphetamines, barbiturates, benzodiazepines, benzoyllecgonine, opiates, phencyclidine, and tricyclic antidepressants. The pediatric neurology service was also consulted and performed an electroencephalogram while the patient still had opisthotonus, tongue fasciculations, and hyperreflexia. Results revealed normal electrical activity without evidence of seizure activity.

The patient did not have any further episodes of increased muscular tone and was not given any other medications during the PICU stay. He was transferred to a regular ward after 6 hours of PICU observation. We reevaluated him 20 hours after the ingestion, and he was completely asymptomatic. He was restarted on formula feeds without difficulty. The child was discharged from the hospital the next day.

DISCUSSION

4-AP is an orphan drug used in the United States mainly to treat disorders of neuromuscular transmission. The drug acts by blocking the potassium channels. This inhibition prevents K^+ efflux and thus prolongs the action potential. The net effect is an increase in acetylcholine release at the neuromuscular junction and an increase in muscle strength. It is also believed that 4-AP may have a direct role in the modulation of calcium. 4-AP crosses the blood-brain barrier. Some authors have postulated that the seizures seen in these patients are attributable to increased norepinephrine turnover or to increased acetylcholine release.¹⁵ The compound also stimulates the release of excitatory neurotransmitters in the spinal cord. For this reason, the aminopyridines have been used to improve function in patients with spinal cord injury.

The direct muscular stimulation by 4-AP varies with species and tissue. In humans, a direct muscular effect has not been conclusively found.

The chloride salt of 4-AP is a water-soluble, odorless tan-to-white crystal. The structure consists of a pyridine ring with a single amide in the 4 position. The activity of the compound seems to be more dependent on the amino group, because it has been observed that substitution onto this group removes the activity of the compound.¹⁵

The compound has a rapid gastrointestinal absorption.⁴ Studies have shown 2 serum peaks after intravenous administration, one immediately after the injection and the second 20 to 90 minutes after the injection.¹⁶ Studies also suggest a large volume of distribution based on prolonged plasma decay curves.¹⁶ It is known that 87% of the drug is excreted unchanged in the urine; therefore, only a small amount of 4-AP will undergo biotransformation.¹⁵

Human therapeutic doses range from 7.5 to 200 mg/d in single or divided doses. According to one study, a serum concentration between 30 to 59 ng/mL produces the best therapeutic response without significant toxicity.¹⁷ The most commonly reported signs of toxicity with 4-AP are tremor, hyperexcitability, salivation, seizures, and extrapyramidal symptoms.^{4,18,19} Seizures have been reported at se-

rum levels as low as 104 ng/mL.²⁰ Although the acute effects of the drug in an overdose are dramatic, no long-term effects have been reported in animals or humans.

There have been few reported cases of 4-AP intoxication. Spyker and colleagues⁴ wrote one of the earliest reports of 4-AP poisoning in 1980. They reported 3 male patients who had ingested "pinch amounts" of an avicide containing 99% 4-AP in the belief that it was Spanish fly (cantharidin). Two of them were hospitalized. Both of these patients reportedly developed weakness, nausea, profuse perspiration, and very mild elevations in serum glutamic oxaloacetic transaminase. One of these men had multiple episodes of generalized tonic-clonic convulsions. In this case report, an EEG performed on the fourth hospital day was interpreted as normal. Both patients made full recoveries.

Stork and Hoffman¹⁸ reported 3 cases of overdose by adult patients with multiple sclerosis who were on 4-AP therapy. All the patients had witnessed tonic-clonic convulsions, and one of them developed status epilepticus lasting for 40 minutes. All of the patients required intubation, but none of them had reported permanent sequelae. The results of EEG and hepatic transaminases were not reported by the authors. The treatment used for the seizures in these patients included benzodiazepines, phenytoin, and phenobarbital.

In 1996, Pickett and Enns¹⁹ described a case of a 34-year-old woman with multiple sclerosis who had doubled her usual daily 4-AP dosing regimen. Approximately 4 hours after her second daily dose she noted that she felt "giddy" and developed involuntary movements of her extremities. These movements were noted to be choreoathetoid in nature. In between episodes she was reported to be coherent. This case does not mention whether an EEG was performed. The effects lasted for ~1 hour. As in the other cases, she was treated with benzodiazepines and had a full recovery.

3,4-Diaminopyridine is a structurally related compound that has also been used for disorders of neuromuscular transmission.²¹ Studies suggest that it is more potent and has fewer side effects than 4-AP. However, seizures were reported in a patient who was taking 3,4-diaminopyridine for Eaton-Lambert syndrome and inadvertently received a higher dose of this medication.²¹ Despite suffering cardiac arrest, she survived and recovered completely. It is reasonable to treat these 2 drugs in a similar fashion. Their toxicity seems to be equivalent.

To our knowledge, this case is the first reported pediatric intoxication with 4-AP. The use of 4-AP and some structurally related drugs has increased in the past decade, which translates into greater potential for poisoning and overdose to occur with this medication.

The clinical effects displayed in our patient are consistent with previously reported cases in adults. However, in this case an EEG was performed shortly after ingestion and while the patient was still symptomatic. It failed to show evidence of seizure activity, although the patient was displaying convulsive

movements. This suggests that this neuromuscular effect is not produced by epileptogenic activity in the brain but perhaps at the level of the spinal cord or at the neuromuscular junction. Given reports of extrapyramidal symptoms described above, one may also consider that these patients are experiencing dystonic activity.

When an overdose with 4-AP is encountered, it is important that these patients be evaluated at a health care facility. The initial treatment for patients with 4-AP overdose includes early decontamination and activated charcoal in an attempt to reduce drug absorption. Because the drug has a very rapid gastrointestinal absorption, the use of decontamination in cases that present later is of negligible value. Muscular irritability should be treated with benzodiazepines, titrated to improvement or resolution of the symptoms. It has been suggested that phenytoin is an effective agent for the control of 4-AP induced convulsions, but clinical data about its use are limited.^{20,22} The data available on the utility of phenytoin are from a mouse study done by Yamaguchi and Rogawski.²² They found that drugs like phenytoin, carbamazepine, phenobarbital, and valproate were protective against 4-AP induced-seizures, whereas gamma aminobutyric acid enhancers like the benzodiazepines were not protective. Like most animal data, it is difficult to extrapolate these findings to human cases.

All patients with a history of an ingestion should be observed for signs and symptoms of toxicity. Because of the rapid absorption and onset of action of the drug, 6 to 8 hours of observation are reasonable. Patient with symptoms of toxicity should be admitted to the hospital. One of the risks of this ingestion is ventilatory failure. Because of this potential complication, these patients should be treated in an institution capable of managing the pediatric airway. A PICU should be available for patients who are symptomatic.

Based on what is known about 4-AP's pharmacology, neuromuscular blockade may be useful in cases where adequate control of excessive muscular activity cannot be achieved with anticonvulsants. Serum or urine levels are difficult to obtain and will not help in the emergency management of these patients.

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