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4-Aminopyridine Toxicity: a Case Report and Review of the Literature

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Abstract

Introduction 4-Aminopyridine (4-AP) selectively blocks voltage-gated potassium channels, prolongs the action potential, increases calcium influx, and subsequently, enhances interneuronal and neuromuscular synaptic transmission. This medication has been studied and used in many disease processes hallmarked by poor neuronal transmission in both the central and peripheral nervous systems including: multiple sclerosis (MS), spinal cord injuries (SCI), botulism, Lambert-Eaton syndrome, and myasthenia gravis. It has also been postulated as a potential treatment of verapamil toxicity and reversal agent for anesthesia-induced neuromuscular blockade. To date, there have been limited reports of either intentional or accidental 4-AP toxicity in humans. Both a case of a patient with 4-AP toxicity and review of the literature are discussed, highlighting commonalities observed in overdose.

Case Report A 37-year-old man with progressive MS presented with diaphoresis, delirium, agitation, and choreoathetoid movements after a presumed 4-AP overdose. 4-AP concentration at 6 h was 140 ng/mL. With aggressive benzodiazepine administration and intubation, he recovered uneventfully.

Discussion The commonalities associated with 4-AP toxicity conforms to what is known about its mechanism of action combining cholinergic features including diaphoresis, altered mental status, and seizures with dopamine-related movement abnormalities including tremor, choreoathetosis, and dystonia. Management of patients poisoned by 4-AP centers around good supportive care with definitive airway management and controlling CNS hyperexcitability aggressively with

gamma-aminobutyric acid agonist agents. Adjunctive use of dopamine antagonists for extrapyramidal effects after sedation is a treatment possibility. As 4-aminopyridine recently received Federal Drug Administration approval for the treatment of ambulation in patients with MS, physicians should be keenly aware of its presentation, mechanism of action, and management in overdose.

Keywords 4-Aminopyridine · Case report · Overdose · Toxicity

Introduction

4-Aminopyridine (4-AP) selectively blocks voltage-gated potassium channels, prolongs the action potential, increases calcium influx, and subsequently, enhances interneuronal and neuromuscular synaptic transmission. 4-AP was initially developed in the 1960's as an avicide (Avitrol®). When consumed, 4-AP causes birds to emit distress calls secondary to involuntary diaphragmatic contractions. When used properly, it is reported to only actually kill about 1 % of the animals [1, 2].

4-AP enhances the release of acetylcholine from nerve endings and has been shown to increase dopamine transmission in rat striatum [3–7]. Furthermore, it is frequently used as an experimental agent to induce seizures. Given its unique mechanism, 4-AP has been studied and used in many disease processes hallmarked by poor neuronal transmission. It has been employed with variable success for processes that affect the neuromuscular junction such as: Lambert–Eaton syndrome, myasthenia gravis, saxitoxin and tetrodotoxin-induced paralysis, anesthesia-induced neuromuscular blockade, and botulism [8–13].

In demyelinated neurons, 4-AP has been shown to improve both axonal conduction and synaptic transmission

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and, therefore, is of theoretical therapy for spinal cord injury (SCI) [14, 15]. Unfortunately, research regarding its efficacy in SCI has been inconclusive. Although animal models and some early studies reported improvement in function and sensation, subsequent randomized, placebo-controlled studies have not demonstrated clinically significant benefits [16–22]. Summative interpretation of these results is difficult due to small numbers, mixed patient populations and variations in duration, dosage, and mechanism of administration. As a consequence, the Spinal Cord Injury Rehabilitation Evidence Research Team is currently unable to endorse the use of 4-AP for SCI based on available evidence [23].

In 2010, 4-AP received FDA approval to improve ambulation in patients with multiple sclerosis (MS). Multiple phase II and III trials have demonstrated improvement in both walking speed and function in about one third of patients [24]. The currently approved dosing regimen is 10 mg by mouth twice daily. In a dose-ranging study, administration was discontinued due to adverse effects at doses greater than 25 mg; seizures occurred in two patients taking 30 and 35 mg twice daily [25]. In therapeutic study doses, 4-AP has an estimated volume of distribution of 2.5 L/kg, a serum clearance of 0.6 L/h/kg and a terminal half-life of 3.6 h. Protein binding is negligible [26]. There are currently no data regarding the use of enhanced or extracorporeal elimination. As expected, the extended-release formulation has a longer half-life (5.7–6.9 h) [27].

4-AP is mechanistically appealing as a potential treatment of calcium channel blocker poisoning. 4-AP facilitates calcium conductance by blocking potassium channels on the cytoplasmic side of the cellular membrane, causing depolarization and opening of voltage-gated calcium channels. Rodent and feline models have displayed improvement of hemodynamic outcomes with infusion doses of 2 mg/kg [28–30]. The 1 mg/kg dose did produce improvements in verapamil-poisoned dogs but not in other animals [28–31]. In a rodent model of verapamil poisoning, Graudins and Wong demonstrated that cardiac output and blood pressure improved with 4-AP alone and in combination with levosimendan. However, an additive effect of 4-AP and levosimendan on hemodynamics was not seen [32]. Nevertheless, case series demonstrating the effectiveness of 4-AP in the treatment of severe calcium channel blocker toxicity in humans have been published [33–36].

4-AP toxicity has been studied in many mammalian species and produces a usual sequence of signs and symptoms: hyperexcitability, salivation, tremors, diaphoresis, convulsions, and cardiac arrest [37, 38]. To date, there have been limited reports of either intentional or accidental 4-AP toxicity in humans [39–48]. Both a case of a patient with 4-AP toxicity and review of the literature are discussed, highlighting commonalities observed in overdose.

Case Report

A 37-year-old man with a medical history of chronic progressive MS and depression was transferred to a local emergency department (ED) after he was found by his brother naked and confused on the floor. He had pills in his mouth and scattered about his person. The brother had left the patient in his usual state of health for approximately 1 h prior to finding him in this condition. The patient's prescribed medications included: 4-aminopyridine, paroxetine, and fingolimod. Serum electrolytes were normal, and acetaminophen, salicylate, and ethanol levels were unmeasurable. Total creatinine phosphokinase measured 116 U/L (<200 U/L), and white blood count measured $10,100/\text{mm}^3$ ($3.8\text{--}10.3 \times 10^3$) with 89 % neutrophils. Electrocardiogram was normal except for sinus tachycardia. In the ED, the patient was administered intravenous (IV) fluids and 10 mg IV lorazepam and then transferred to a tertiary care hospital for definitive management.

Upon arrival to the tertiary care hospital ED, initial vital signs included: blood pressure, 125/104 mmHg; heart rate, 133 bpm; respiratory rate, 30 breaths per minute; oral temperature, 36.8 °C; and room air SpO₂ of 97 %. Physical examination revealed the patient to be agitated and delirious with slurred and incomprehensible speech. Other notable physical exam findings included: mid-range and reactive pupils, dry mucous membranes, diffuse diaphoresis, choreoathetoid movements, and tremulousness with 2+ deep tendon reflexes in the upper extremities and 3+ in the lower extremities without clonus. A non-contrasted brain computed tomogram was normal. A comprehensive urine drug screen by gas chromatography–mass spectrometry identified small amounts of diphenhydramine, caffeine, nicotine, and acetaminophen metabolites. While in the ED, he was placed in soft restraints, administered IV fluids and a total of 110 mg IV diazepam and 50 mg IV diphenhydramine (for possible dystonia) over a 2-h period with some improvement in agitation.

The patient was admitted to the intensive care unit (ICU) and, due to persistent agitation and delirium that was difficult to control despite an additional 20 mg IV diazepam, he was endotracheally intubated and sedated with IV propofol 2 h after admission to the ICU. An electroencephalogram (EEG) revealed no epileptiform activity. The patient grimaced to strong tactile stimuli. He had gradual improvement of his mental status over the subsequent two hospital days (HD) and was extubated uneventfully on HD three. After extubation, the patient exhibited paranoid behavior and stated that people were “coming after me, hurting me, and taking my pills.” This behavior gradually ameliorated, and the patient was transferred home in his baseline state on HD seven after psychiatric evaluation. A 4-AP level obtained approximately 6 h after his ingestion measured 140 ng/mL

(17.3–42.7 ng/mL) with a subsequent concentration approximately 24 h later measuring 6 ng/mL. Interestingly, the patient's brother later reported that since the initiation of 4-AP, the patient had been exhibiting increasingly psychotic behavior.

Case Report Toxicity Review

In 1978, Spyker et al. reported one of the first cases of acute 4-AP poisonings in three manufacturing employees who mistook 4-AP for Spanish fly and ingested it during a morning coffee break. The first patient developed intense diaphoresis, agitation, “convulsive-like movements”, tachycardia, and three generalized tonic–clonic seizures. He was treated with intubation, ventilation, diazepam, naloxone, gastric lavage, sodium bicarbonate, and a sodium cathartic. He was discharged on HD five. The second patient was noted to have “profuse perspiration” as well as a fluctuating mental status including disorientation, combativeness, and unconsciousness. He was likewise treated with gastric lavage, activated charcoal, a sodium cathartic, fluids, and mannitol. The third employee successfully induced vomiting within 10 min of ingestion and had no “adverse effects” [39].

In 1979 during an outbreak of *Clostridium botulinum* type E from tinned Alaskan salmon, four elderly patients were treated with intravenous 4-AP. Restoration of evoked peripheral muscle action potentials and power was noted. 4-AP did not, however, improve ventilatory muscle power. Interestingly, seizures were reported in two patients after discontinuation of the 4-AP infusion, and they received 60–80 mg diazepam. Serum levels in the two patients who developed seizures ranged between 30 and 475 ng/mL during the infusion. One patient with seizures and another without died of “sudden respiratory obstruction” and “bronchopneumonia and severe metabolic acidosis” [14].

Stork and Hoffman in 1994 published a case series of three patients with 4-AP overdose resulting in seizure activity. The first case described a 28-year-old woman with MS who consumed extra 4-AP in attempts to ameliorate increased lower extremity weakness. The patient experienced two seizures and was treated with diazepam, lorazepam, phenytoin, activated charcoal, and intubation. A 4-AP concentration measured 136.3 ng/mL. The second case described a 54-year-old woman who suffered two seizures after being started on an escalating dose of 4-AP (exact dose unknown). The third patient was a 52-year-old woman with MS and developed 40 min of status epilepticus. She was treated with diazepam, phenytoin, and phenobarbital. No long-term adverse outcomes were reported in any of the patients [41].

In 1995, Pickett and Enns reported the first case of extrapyramidal manifestations of 4-AP toxicity. They described a

34-year-old woman with MS who increased her dose in anticipation of extra activity during the day and developed “tremulous dystonic and choreoathetoid-type writhing of the extremities.” She had a fixed stare, slurred speech, confabulation, and delirium. She was treated with lorazepam which caused a “rapid cessation of the shaking”, and the involuntary movements improved over 1 h. Vital signs included: pulse, 90 bpm; blood pressure, 129/61 mmHg; respirations, 36 breaths/min; and oral temperature, 33.8 °C. The authors inferred that the hypothermia was likely factitiously low in the setting of tachypnea. This patient's measured concentration was 233.6 ng/mL [42].

Smeets and Kunst in 1995 described a case of accidental 4-AP intoxication of a 22-year-old man who mistakenly took the medication assuming it was a bodybuilding supplement given its name contained “amino.” He was reported to have developed cardiac dysrhythmias, transient right bundle-branch block, accelerated idioventricular rhythm, and “severe” hypertension. The serum concentration was measured at 335 ng/mL [43].

The first pediatric exposure resulting in toxicity was reported by Velez et al. in 2003. The subject of their paper was an 8-month-old boy who was found with greenish saliva next to a capsule with green 4-AP powder missing. The boy was tachycardic and tachypneic and developed “dramatic opisthotonic posturing and vermiform tongue fasciculations.” An EEG did not demonstrate seizure activity, and the patient fully recovered within 20 h [44].

In 2006, Johnson and Morgan reported a second case of cardiotoxicity in the setting of 4-AP ingestion. A 56-year-old man rubbed 4-AP on a sore tooth after he had noted the local anesthetic effects on his tongue and throat after taking it for peripheral neuropathy. He was found by his son 1 h after ingestion, diaphoretic, and delirious with unintelligible speech. He developed hypothermia to 32.8 °C and atrial fibrillation with rapid ventricular response. He was treated with intubation, cardioversion, and rewarming and fully recovered. The cause of both the hypothermia and atrial fibrillation remained enigmatic [45].

In 2008, Burton and colleagues described a case series of four patients who were admitted to the hospital for status epilepticus after an unintentional overdose of 4-AP secondary to a compounding error by a Canadian pharmacy. All developed symptoms within minutes to hours of ingestion. All patients were intubated and received benzodiazepines and phenytoin. One patient subsequently died from a prolonged hospital stay and “systemic complications” [46].

In 2009, De Cauwer et al. reported a third case of a patient with 4-AP toxicity associated with extrapyramidal symptoms. A 45-year-old woman ingested 35 mg of 4-AP in three doses over 10 h and was found by her daughter unresponsive with a fixed stare. She was shaking and exhibited choreoathetoid movements. She was also noted

to have slurred speech with confabulation. Unique to this case was the fact that the patient had reappearance of her symptoms almost immediately after re-initiation of 4-AP and additionally developed opisthotonus and risus sardonicus [47].

A fourth case of a patient experiencing extrapyramidal dysfunction was reported by Badruddin et al. in 2009. They described a case of a 22-year-old man with MS who ingested 300 mg of 4-AP. He was agitated, diaphoretic, flushed, febrile hypertensive, and also experienced supraventricular tachycardia. He was intubated, and an EEG showed frequent “diffuse polyspike and spike-wave discharges.” Echocardiogram demonstrated a hypokinetic myocardium with an ejection fraction of 24 % that later normalized. Five days after the overdose, he was bradykinetic, weak (1/5 on the Ashworth scale), sustained “profound” memory loss, and spoke rarely and quietly. These symptoms slowly improved with therapy over a period of months; however, he continued to have difficulty with short-term memory and learning new tasks. Magnetic resonance imaging (MRI) of the brain demonstrated increased signal intensity in both medial temporal lobes and the anterior cingulum (baseline MRI prior to overdose did not have these changes). The clinical presentation resembled autoimmune-mediated limbic encephalitis [48].

Finally, in 2011, Schwam reported 4-AP toxicity attributed to a compounding error in a 42-year-old man with a C3 SCI. He was noted to have abdominal pain, profuse diaphoresis, hypersalivation, and choreoathetosis followed by status epilepticus. This unfortunate gentleman had a prolonged and complicated hospital course including sepsis, gastrointestinal bleeding, non-ST segment elevation myocardial infarction and intracranial hemorrhage. He developed permanent amnesia. [49].

Discussion

A summary of cases with documented toxicity related to 4-AP is shown in Table 1. There appears to be a fairly consistent constellation of signs and symptoms observed in the setting of 4-AP toxicity: diaphoresis, neurologic excitability, gastrointestinal effects, and cardiac toxicity.

Extrapyramidal movement abnormalities—ranging from bradykinesia to choreoathetosis to opisthotonus—have been independently reported. Other manifestations of neural excitability including confabulation, agitation, paresthesias, and tremor are likewise commonly described. Neurologic side effects that have been reported in study populations with variable frequency include: dizziness, ataxia, insomnia, and lightheadedness [9, 50–55]. There have been two reports of long-term memory difficulties in patients after overdose, but no long-term effects have been reported with therapeutic use [48, 49, 52].

Seizures occur commonly with 4-AP toxicity and can progress to status epilepticus. The reported incidence of seizures with therapeutic use ranges between 1 and 3 %, which is comparable to the baseline incidence of seizures in patients with MS [56–58]. In clinical trials of the extended-release formulation of 4-AP, seizures appear to be dose related [27, 40, 55]. Seizures have been observed with 4-AP concentrations ranging between 30 and 475 ng/mL [14, 41]. In contrast, 4-AP concentrations up to 114 ng/mL have been measured in study participants without serious effect while a seizure was reported in a study participant with a level of 104 ng/mL [59, 60]. In the same study, an “acute confusional episode” without seizure was reported at a concentration of 114 ng/mL [59]. With respect to 4-AP concentrations obtained in the setting of overdose, the timing of measured blood concentrations in relation to the ingestion is often unclear. Based on the available literature, serum 4-AP concentrations appear helpful in establishing exposure yet unreliable in accurately assessing clinical toxicity.

Various cardiac effects have been described with 4-AP toxicity and include: hypertension, supraventricular tachycardia, atrial fibrillation, bradycardia, and diffuse myocardial hypokinesia. The associated atrial fibrillation in the one patient described above is difficult to interpret as this patient was concomitantly hypothermic which may have caused myocardial irritability. There is a theoretical concern for QT prolongation through inhibition of the hERG potassium channel as 4-AP is a potassium channel blocker. Using terfenadine as a control, 4-AP was evaluated in concentrations ranging from 0.1 to 30 mM in human embryonic kidney 293 cells transfected with the hERG gene. At three orders of magnitude higher than expected therapeutic plasma concentrations, 50 % inhibition was observed. The authors concluded that at therapeutic doses, 4-AP has low potential for prolonging QT interval or inducing Torsades de pointes [61]. This mirrors reported clinical experience in both therapeutic trials and overdose. Several studies have documented a lack of effect on cardiac repolarization in both therapeutic and supratherapeutic doses [51, 62, 63]. Reports of death were not due to acute cardiotoxicity but rather acquired respiratory disease (e.g., ventilator-associated pneumonia) and complications related to a prolonged hospital course [14, 46].

4-AP has other miscellaneous toxicities. Gastrointestinal effects such as dry mouth, nausea, and vomiting are relatively common; elevated liver enzymes have been reported [52]. Diffuse, profound diaphoresis is common. Hematologic effects include thrombocytopenia. Posterior tibial artery vasospasm was discussed in one case and was successfully treated with oral nifedipine [20].

Seizure activity was not observed or documented in the patient described in this manuscript. Taking into account the

Table 1 Cases with documented toxicity related to 4-AP

Study	4-AP concentration	Seizure	Neurological	Cardiovascular	GI	Skin	Treatment	Intubation
Spyker et al.	Pt 1: Not obtained Pt 2: Not obtained	Pt 1: Yes Pt 2: No	Pt 1: Agitation, convulsive-like movements; resolved Pt 2: Disorientation, combativeness, unconsciousness; resolved Botulism	Pt 1: Tachycardia Pt 2: Not described	Pt 1: Abdominal pain, nausea Pt 2: Abdominal pain, nausea	Pt 1: Diaphoresis Pt 2: "Profuse perspiration"	Pt 1: Diazepam, naloxone, gastric lavage, sodium bicarbonate, and a sodium cathartic Pt 2: Gastric lavage, activated charcoal, a sodium cathartic, fluids, and mannitol 60–80 mg diazepam	Pt 1: Yes Pt 2: No
Ball et al.	35–475 ng/mL	Yes in 2/4 patients	Botulism	ND	ND	ND		Previously intubated
Stork and Hoffman	Pt 1: 136.3 ng/mL Pt 2: ND Pt 3: ND	Pt 1: Yes Pt 2: Yes Pt 3: Status epilepticus	Pt 1: Obtunded, post-ictal left sided weakness; resolved Pt 2: Lethargic; resolved Pt 3: ND	Pt 1: Tachycardia Pt 2: ND Pt 3: ND	Pt 1: ND Pt 2: ND Pt 3: ND	Pt 1: ND Pt 2: ND Pt 3: ND	Pt 1: Charcoal, phenytoin, Pt 2: Benzodiazepine, phenytoin Pt 3: Phenytoin, benzodiazepine, phenobarbital	Pt 1: Yes Pt 2: Yes Pt 3: ND
Pickett and Enns	233.6 ng/mL	No	"Giddy", tremulous choreoathetoid-type writhing of the extremities, facial grimace, slurred speech, and confabulation	Normal	Nausea	ND	Lorazepam, Naloxone, prochlorperazine, activated charcoal	No
Velez et al.	ND	No	Opisthotonic posturing, increased muscle tone, vermiform tongue fasciculations	Tachycardia	ND	ND	Charcoal, cathartic, midazolam	No
Johnson and Morgan	ND	No	hyperreflexic	Atrial fibrillation with cardioversion	Vomiting	Diaphoretic	Passive warming, cardioversion	Yes
Burton et al.	ND	Four patients experienced status epilepticus	Unintelligible speech, left facial droop	ND	ND	ND	Benzodiazepines, phenytoin	Yes
DeCauwer H et al.	ND	No	Four patients with unusual sensory and behavioral symptoms	Tachycardia	ND	ND	Depakine, rechallenge of 4AP caused recurrence of symptoms	No
Badruddin et al.	ND	No	Dystonic choreoathetoid-type movements, opisthotonus, confusion, confabulation	SVT, Hypertension, diffuse hypokinesia	ND	Cool, flushed, diaphoretic	Rehabilitation	Yes

Table 1 (continued)

Study	4-AP concentration	Seizure	Neurological	Cardiovascular	GI	Skin	Treatment	Intubation
Schwam	ND	Status	hypophonic lucid speech, antero- and retrograde amnesia Agitation, choreathetosis, persistent antero- and retrograde amnesia	HTN, bradycardia	Abdominal pain	Profuse diaphoresis	Lorazepam, phenytoin	Yes

ND not documented, HTN hypertension, SVT supraventricular tachycardia

fact that this patient received diazepam, lorazepam, and propofol, perhaps this propensity was halted or not allowed to progress in any observable manner. Reviewing other case reports, benzodiazepines and other anticonvulsants were administered in reaction to seizures as opposed to aggressively treating the symptoms associated with neurologic hyperexcitability. In a murine model that studied the benefits of pretreatment with phenytoin, carbamazepine, felbamate, zonisamide, phenobarbital, and valproate protected against 4-AP-induced seizures, and diazepam, ethosuximide, and vigabatrin did not [64]. In humans, however, there are little data to either support or refute the use of anticonvulsants to treat seizures in the setting of 4-AP toxicity.

Usual methods of decontamination and enhanced elimination were not utilized in this patient's care. Although, activated charcoal and gastrointestinal decontamination have been used in patients with 4-AP overdose, insufficient data exist regarding improvement in outcome and cannot be routinely recommended. Moreover, given the propensity for the 4-AP-poisoned patient to seize, charcoal aspiration is a significant concern. There are no data regarding extracorporeal elimination; it is unlikely, however, if this method of elimination would be helpful given the drug's volume of distribution.

Regarding the other xenobiotics to which this patient was exposed, fingolimod is prescribed as a disease-modifying therapy for MS that reduces the infiltration of lymphocytes into the CNS. The drug's only adverse CNS effects are those secondary to opportunistic neurotropic viruses [65]. The patient's unusual and protracted clinical manifestations were not consistent with the generally benign course of paroxetine toxicity, and also, the lack of lower extremity clonus made serotonin syndrome less likely. However, paroxetine is not detected in the authors' gas chromatography/mass spectroscopy comprehensive drug screen library and is therefore a limitation.

Conclusion

This case report highlights the commonalities noted in previous case reports and series including profound diaphoresis, extrapyramidal symptoms, and delirium. He was treated with aggressive administration of benzodiazepines and intubation with complete recovery. Management of patients poisoned by 4-AP centers around meticulous and aggressive supportive care with definitive airway management and controlling CNS hyperexcitability with sedatives such as benzodiazepines or similar gamma-aminobutyric acid agonist agents. Adjunctive use of dopamine antagonists for extrapyramidal effects after aggressive sedation is a treatment possibility. Insufficient data exists to routinely recommend

phenytoin, activated charcoal, or extracorporeal elimination. Discussion with the regional poison center and medical toxicologist is recommended for all cases of 4-AP toxicity to assist in appropriate management.

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