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VETERINARY TOXICOLOGY

A Review of 29 Incidents Involving 4-Aminopyridine in Non-target Species Reported to the ASPCA Animal Poison Control Center

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Abstract 4-Aminopyridine (4-AP) is an avicide used in products that are approved by the Environmental Protection Agency (EPA) to control populations of various birds. Pharmaceutical 4-AP is also used in humans to treat neural and muscular dysfunctions associated with multiple sclerosis. Although strict restrictions for its use are in place, exposures to 4-AP bait by non-target species still occur. Twenty-nine exposures of 4-AP bait involving non-target species were identified and retrieved from the ASPCA Animal Poison Control Center medical record database. Canines were the most commonly exposed (86 %) species followed by felines (10 %). The highest frequency of exposures was reported from Colorado (22 %). Most commonly reported clinical signs in canines were tremors, hypersalivation, seizures, tachycardia, and ataxia. The onset time of signs ranged from 5 to 300 min with an average of 89 min. Clinical signs lasted from 15 to 84 h with an average of 37 h. Patient outcome was known in six cases; one dog died 4 h after the exposure and five made full recovery with supportive care. Treatment of five surviving patients included administration of activated charcoal, use of anticonvulsants and muscle relaxants like diazepam and methocarbamol, and intravenous fluids. Diagnosis of 4-AP toxicosis can be supported by testing the gastric contents of the exposed patient. Due to the rapid absorption, samples need to be collected and frozen/chilled promptly. For successful patient outcome, treatment must be implemented quickly after an exposure.

Keywords 4-Aminopyrdine · Toxicity · Canine · Non-target animal species · Treatment

The information in this article has not been previously presented.

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Introduction

4-Aminopyridine (4-AP) is an avicide used in products that are approved by the Environmental Protection Agency (EPA) to control populations of red-winged, yellow-headed, rusty, and Brewer's blackbirds, grackles, cowbirds, pigeons, and starlings in, on, or in the areas of feedlots, structures, nesting, roosting, landfills, airports, and feeding sites [1].

The 4-AP is also used in humans to treat neural and muscular dysfunctions associated with multiple sclerosis. It enhances transmission at synapses including the neuromuscular junction and is currently approved by the FDA to help improve walking in patients with multiple sclerosis [2]. It has also been used for treating clinical signs associated with Eaton–Lambert syndrome, botulism, and myasthenia gravis [3–5]. The medication is available in 10-mg tablets with the brand name of AMPYRA™.

As bird control bait, 4-AP is available as treated corn, treated corn pieces, and mixed grains in 0.5 or 1 % concentrations with a brand name of Avitrol®. EPA registration of powdered formulations was voluntarily cancelled in 2007 [1]. 4-Aminopyridine is highly toxic to mammals, fish, and birds and is therefore classified federally as restricted-use pesticides, meaning that it can only be purchased and used by a certified applicator [1]. Sometimes promoted as a bird flock frightening agent or repellent, the certified applicator must supervise the application site while the bait is placed out and immediately remove any remaining bait and dead birds once the treatment time is completed [1]. Some state and local laws may be more restrictive [1].

Although strict restrictions for its use are in place, accidental exposures to 4-aminopyride-containing bait by non-target species like humans and domestic or wild animals still occur. The presence of corn or other grains in the bait may attract non-target species such as dogs to eat the bait after it has been spread or while it is being stored prior to its use. This article

examines incidences of non-target species exposures to 4-AP pesticide reported to the ASPCA Animal Poison Control Center from 2002 to 2011. The article also provides treatment overview of 4-AP toxicosis in dogs and cats.

Case Reports: ASPCA Animal Poison Control Center Data (2002–2011)

A search of the ASPCA Animal Poison Control Center (APCC) database showed the presence of 29 exposures to non-target species involving 4-AP bird bait from 2002 to 2011. The search involved exposure to only one agent; cases involving multiple exposures were removed from the search. Out of 29 exposures, the most common non-target species was canines (n =25; 86 %), followed by felines (n =3; 10 %), and bovines (n =1; 3 %). Canine weights ranged from 1.8 to 38.6 kg with an average of 19.6 kg. Canine ages ranged from 0.3 to 13 years with an average of 3 years. The location of the exposure was known in 27 incidences, and the highest frequency of exposures was reported from Colorado (n =6) followed by Nevada (n =5), Arizona (n =3), and Pennsylvania (n =3). Of the 29 exposures, 14 were assessed by the APCC staff as toxicosis or suspected toxicosis, meaning that the history of exposure, the time of onset of clinical signs, and the types of clinical signs were consistent with 4-AP toxicosis. These 14 cases involved canines, and the most commonly reported clinical signs following exposure were tremors (n =5; 35 %), hypersalivation (n =5; 35 %), seizures (n =4; 29 %), tachycardia (n =3; 21 %), and ataxia (n =3; 21 %). The onset time of signs after an exposure was known in 13 of the 14 cases and ranged from 5 min to 5 h with an average onset time of 89 min. The patient outcome and duration of signs were known in 6 of the 14 cases. One death was reported 4 h after the exposure. Five patients made a full recovery with provision of supportive care. The clinical signs in the affected patients lasted for 15 to 84 h after the exposure with an average of 37 h. Treatment of the five patients that survived included administration of activated charcoal, use of anticonvulsants and muscle relaxants like diazepam and methocarbamol, and supportive care consisting of intravenous fluids.

Discussion

Although the mechanism is not fully understood, 4-AP is known as a potassium ion channel blocker that increases the release of acetylcholine release at the neuromuscular junction and in the central nervous system (CNS). The net effect of this action is enhancement of cholinergic activity. In mammals, the clinical signs of hyperexcitability, salivation, tremors, muscular incoordination, cardiac or respiratory arrest, and death can be seen after an acute oral toxic exposure [6]. In humans, three adult males experienced immediate burning of the throat and abdominal discomfort within 15 min after ingesting a pinch of 99 % pure 4-AP by mistake in a manufacturing plant followed by development of nausea, vomiting, weakness, dizziness, diaphoresis, and convulsive-like movements [7]. Two patients were aggressively treated in the hospital with activated charcoal, diazepam, and intravenous fluids and discharged within 4 and 5 days of exposure [7]. The third man successfully induced vomiting on himself within 10 min of ingestion and did not report any additional adverse effects [7]. In this study, similar treatments were shown to be effective for dogs.

4-Aminopyridine is rapidly and completely absorbed orally but poorly absorbed dermally [8]. One study found that the onset of clinical signs is generally within 10–15 min after an oral exposure with death occurring 15 min to 4 h later at doses near the LD_{50} [8]. On average, in this study, the onset of clinical signs was longer than what has been published previously. One possible reason could be the difference in doses of 4-AP these animals were exposed to. Although ingested dosages could not be calculated in this study, it is possible that the delay in the onset of clinical signs was due to animals ingesting dosages below the reported LD_{50}. 4-AP is considered an effective bird repellent because as a flock feeds on the treated corn mixture, a small number of birds become symptomatic. Other birds in the flock interpret the symptomatic birds' signs as a distress call and flee the area. When used per label directions, less than 4 % of birds in a flock are expected to be killed because treated corn is diluted with untreated corn and spread. Dogs have been shown to be particularly sensitive to 4-AP with an oral LD_{50} of 11.9 mg of 4-aminopyridine per kilogram BW after ingesting grain treated with hydrochloric salt and 4 mg/kg when given orally in a capsule [8]. Because commercially available treated corn contained 0.5 % 4-aminopyridine, a 21-kg dog, for example, would need to ingest approximately 50 g of treated corn to reach the oral LD_{50}. Variable oral LD_{50}s in other species have been reported as 20–32 mg/kg in rats and 17.8 mg/kg in pigs [8]. One study estimates the oral lethal dose in horse allowed to ingest treated corn to be between 2 and 3 mg of 4-aminopyridine per kilogram BW [9]. Although limited laboratory data is available, relay toxicity from the acute and long-term ingestion of dead birds that had been feeding on 4-aminopyridine bait is not expected [10]. This is most likely because the 4-AP is rapidly metabolized and eliminated by the bird after ingestion. 4-AP is highly water soluble, so the ingestion of standing water in a baiting area may also pose an exposure risk to non-target species [1].

Tentative diagnosis of 4-AP toxicosis is based on the availability of 4-AP bait, evidence of exposure to the bait, and rapid development of neurologic signs (hyperexcitability, tremors, shaking, ataxia, and seizures). The differential diagnosis list should include other common neurotoxicants causing clinical signs similar to 4-AP in dogs such as CNS stimulants (caffeine

or theobromine); antidepressants (tricyclic antidepressants, selective serotonin reuptake inhibitors); amphetamines or similar agents (metamphetamine, methylphenidate, etc.); decongestants (pseudoephedrine); pesticides like metaldehyde, strychnine, zinc phosphide, organophosphates, and carbamates; and tremorgenic mycotoxins (penitrem A). To aid in diagnosis, gastric contents can be analyzed for 4-aminopyridine at many state laboratories. Due to the rapid absorption and excretion of 4-AP, samples should be collected promptly and labeled. The 4-AP can also be detected in the vomitus, stomach contents, liver, and kidney. Samples can be submitted fresh or frozen depending on the laboratories' recommendations. Call the laboratory to see if they have the capability to analyze 4-AP before sending the samples in for analysis.

Due to its ability to cause rapid onset of neurologic signs, exposure to 4-AP should be considered an emergency and all necessary treatment measures should be carried out quickly. The goals of the treatment are to provide decontamination in asymptomatic animals, stabilize CNS and cardiovascular effects, and provide supportive care in symptomatic patients.

In most situations, animals exposed to 4-AP may already be showing clinical signs when presented to the veterinarians. For such cases, upon presentation, do not induce emesis or administer activated charcoal. Instead, the most important step will be to stabilize the patient first by controlling the CNS and CV effects. Decision to administer activated charcoal can be made after the patient's vital functions have been stabilized.

In a recent exposure, emesis can be induced in an asymptomatic patient using either 3 % hydrogen peroxide solution or apomorphine in dogs or xylazine in cats. The dose of 3 % hydrogen peroxide in dogs is 2.2 ml/kg PO for a maximum of 45 ml. The dose of hydrogen peroxide can be repeated once after 10–15 min if emesis does not work the first time. The dose of apomorphine in dogs is 0.03 mg/kg IV or 0.04 mg/kg IM [11]. Apomorphine in tablet form can also be crushed and dissolved in 0.9 % saline and instilled in the conjunctival sac. Rinse it with water once the emesis has occurred. The dose of xylazine in cats is 0.44 mg/kg IM [11].

Induction of emesis can be followed by administration of activated charcoal. The dose of activated charcoal in dogs and cats is 1–4 g/kg PO [11]. Mix activated charcoal powder with water to make slurry and give it with a gastric tube. Addition of a cathartic to activated charcoal like 70 % sorbitol at 1–3 ml/kg will enhance removal of the bait bound to activated charcoal from the gut [11]. For commercial products, use the labeled dose given on the product. Control vomiting with maropitant citrate (Cerenia®) in dogs and cats (1 mg/kg s/c) before administering activated charcoal to prevent aspiration pneumonia [11].

Various medications can be tried to control muscle tremors, shaking, or seizures in dogs. The best way to control seizures is to use diazepam at 0.5–2 mg/kg IV, repeated as needed [11]. Use pentobarbital sodium intravenously to the effect and repeat as needed if diazepam fails to control seizures. In the authors' experience, the use of the muscle relaxant methocarbamol (55–220 mg/kg IV to effect at a rate no more than 2 ml/min; maximum dose 330 mg/kg/day) is extremely effective in controlling shaking and muscle tremors [11]. Propofol IV bolus in dogs at 1–3.5 mg/kg up to 6 mg/kg followed by a constant rate infusion (CRI) using a syringe pump of 0.1–0.25 mg/kg/min (up to 0.6 mg/kg/min) for 6–12 h and then gradually decreasing can be tired with a maximum duration of propofol CRI of 48 h [11]. If used in cats, carefully monitor PVC and CBC (due to the possibility of developing Heinz body anemia and/or hemolytic anemia) and the propofol dose should be kept as low, and the duration of treatment as short, as possible. Place an intravenous catheter and administer crystalloid fluids intravenously to promote diuresis and maintain normal perfusion of different organ systems. Other treatment measures that may require symptomatic treatment may include monitoring the acid–base status and correcting acidosis using sodium bicarbonate (1–3 mEq/kg IV) [11]. Stabilize the heart rate and blood pressure using a beta-adrenergic blocking agent like propranolol (0.02 mg/kg slow IV; titrate up as needed) or esmolol (0.2–0.5 mg/kg slow IV over 1 min or 25–200 μg/kg/min CRI) [11]. Monitor the body temperature and correct hypothermia (heating pads) or hyperthermia (cooling, fans) if needed. A symptomatic patient may require 1–3 days of aggressive supportive care along with monitoring of the acid–base status, complete blood count, and serum chemistries. Two of the affected human patients with neurologic effects from 4-AP needed 4–5 days of hospitalization. A successful treatment outcome will depend on the dose of the 4-AP and promptness with which the animal was treated after the exposure.

Summary

4-Aminopyridine is a potent avicide regulated by the EPA. Although strict restrictions are in place to prevent exposure of non-target species to 4-AP, the APCC data shows that accidental exposures, especially in dogs, do still occur. For successful patient outcome, aggressive decontamination measures, stabilization of CNS and CV effects, correction of acidosis, and supportive treatment must be implemented quickly after an exposure.

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