The Journal of Veterinary Medical Science

NOTE

Internal Medicine

Accidental afloqualone intoxication in two dogs

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J. Vet. Med. Sci.
80(1): 152–155, 2018
doi: 10.1292/jvms.17-0305

Received: 5 June 2017
Accepted: 31 October 2017
Published online in J-STAGE: 14 November 2017

ABSTRACT. Two dogs presented to the emergency service after accidental ingestion of afloqualone tablets, a muscle relaxant used for back pain in humans. Toxic effects of the drug in these dogs included vomiting, respiratory depression, seizures, ataxia, bradycardia, and hematuria. Treatment consisted of fluid diuresis, furosemide, and propofol. Flumazenil, a gamma-amino butyric acid antagonist, was administered intravenously; however, it was not effective in stopping the seizures in these dogs. Both dogs recovered with supportive treatment. To the authors' knowledge, this is the first documented report of afloqualone intoxication in dogs.

KEY WORDS: afloqualone, canine, flumazenil, intoxication, seizure

Afloqualone [6-amino-2-fluoromethyl-3-(o-tolyl)-4(3*H*)-quinazolinone] is a quinazolinone family gamma-amino butyric acid (GABA)ergic drug and an analogue of methaqualone that was developed in the 1970s. It has muscle-relaxant and sedative effects resulting from its agonist activity at the $GABA_A$ receptor and is commonly used clinically in humans to relieve back pain and spastic muscle disorders [14]. Clinical overdose of GABA agonists in dogs produces symptoms of CNS depression, vocalization, seizure, ataxia, hypersalivation, vomiting, and respiratory and cardiac depression [10]. Afloqualone intoxication in dogs has not been previously reported. However, intoxication by baclofen, barbiturates, and benzodiazepine, which act similarly on GABA receptors, has been published [1, 2, 5, 7, 10, 11]. This report describes two cases of accidental afloqualone intoxication in dogs.

A 4-month-old, intact male Schnauzer weighing 3.5 kg (Dog 1) and a 3-year-old, neutered male Poodle weighing 4.7 kg (Dog 2) were presented to the Veterinary Teaching Hospital of Seoul National University. Dog 1 was presumed to have accidentally ingested more than 100 mg (5 × 20 mg/tablet) afloqualone (Arobest, CJ cheiljedang Corporation, Seoul, South Korea), which were prescribed for the owner. The dog presented to our hospital approximately 15 hr after ingesting the tablets, with a history of vomiting, hypersalivation, and collapsing at home. The owners found the empty pill container in the room with the dog; however, they did not witness the dog ingesting the tablets. Before being admitted to our hospital, the dog was taken to a local hospital, where he was diagnosed with seizures and administered supportive fluid therapy and a diazepam injection. Dog 2 was presented 5 hr after accidental ingestion of 280 mg (14 × 20 mg) afloqualone (Arobest). The owners did not witness the dog ingesting the tablets; however, they found the opened pill container in the room with the dog and 14 tablets were missing. The dog presented with ataxia, vocalizations, and generalized seizures while at home. Two dogs had no previous medical problems.

Upon physical examination, two dogs were dehydrated and normotensive (Doppler blood pressure 130 mmHg [Dog 1], 110 mmHg [Dog 2]). Dog 1 was febrile (rectal temperature, 39.2°C), with a heart rate of 96 beats/min, normal sinus rhythm, and respiratory rate of 42 breaths/min; the dog had a body condition score of 4 out of 9 possible points. Dog 2 was afebrile (rectal temperature, 37.9°C) and bradycardic (heart rate 66 beats/min), with a respiratory rate of 36 breaths/min. Dog 1 was semicomatose and laterally recumbent, with ptyalism, a minimal menace response, and decreased pupillary light reflexes (PLRs). Dog 2 was comatose and had pinpoint pupils and absent PLRs. Most cranial nerve responses were absent or decreased.

Hematological findings of Dog 1 included a normal white blood cell count (9.34×10^3 /μl; reference interval, 5.2–16.0 × 10^3 /μl), decreased red blood cell count (5.0×10^6 /μl; reference interval, 5.7–8.8 × 10^6 /μl), decreased red blood cell specific volume (33.5%; reference interval, 37.1–57.0%), and normal platelets ($176 \times 10^3/\mu l$; reference interval, 143–400 × $10^3/\mu l$). Serum biochemistry revealed mildly elevated alkaline phosphatase (ALP; [176 U/*l*]; reference interval, [8–100 U/*l*]), increased creatine kinase (661 U/*l*; reference interval, 8–216 U/*l*), and mildly decreased creatinine (0.32 mg/d*l*; reference interval, 0.5–1.5 mg/d*l*), with mildly increased glucose (147 mg/d*l*; reference interval, 60–120 mg/d*l*) (Table 1). Dog 1 had red urine, and a urinalysis

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Table 1. Summary of biochemical finding in dogs with afloqualone toxicosis

Parameter	Dog 1	Dog 2	Reference
ALT (U/*l*)	42	45	6–90
AST (U/*l*)	40	NA	10–43
ALP (U/*l*)	176	49	8–100
GGT (U/*l*)	3	2	0–14
TBILI (mg/d*l*)	0.05	0.2	0–0.6
TP (g/d*l*)	5.59	5.2	5.0–7.5
Albumin (g/d*l*)	3.36	2.9	2.6–4.5
GLU (mg/d*l*)	147	213	60–120
BUN (mg/d*l*)	9.9	20	8–30
CREA (mg/d*l*)	0.32	1	0.5–1.5
Ca (mg/d*l*)	11.5	9.2	9.0–11.8
P (mg/d*l*)	5.1	3	2.3–5.5
CK (U/*l*)	661	NA	8–216
Na (mEq/*l*)	143.6	150	145–155
K (mEq/*l*)	4.32	3.7	2.7–5.0
Cl (mEq/*l*)	114.2	113	96–122

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, γ-glutamyltransferase; TBILI, total bilirubin; TP, total protein; GLU, glucose; BUN, blood urea nitrogen; CREA, creatinine; CK, creatine kinase; NA, not assessed.

revealed low urine specific gravity (1.020), proteinuria (1+), hematuria (4+), and hemoglobinuria (4+). Hematological findings of Dog 2 included a normal white blood cell count (7.35×10^3 /μl), red blood cell count (6.34×10^6 /μl), red blood cell specific volume (42.9%), and mild decreased platelet count (131×10^3/μl). Serum biochemistry revealed increased glucose (213 mg/d*l*) (Table 1).

After admission to the intensive care unit, patients monitoring consisted of oscillometric blood pressure (SunTech Medical, Morrisville, NC, U.S.A.), continuous electrocardiography assessment (Datex-Ohmeda, GE Healthcare, Helsinki, Finland), and urinary output via an indwelling urinary catheter with closed collection system.

In Dog 1, initial therapy included administration of a bolus of intravenous fluids (40 m*l* lactated Ringer's solution (LRS; Dai-Han Pharmaceutical, Seoul, Korea), followed by continuous rated infusion of LRS at 5 m*l*/kg/hr. After 1 hr, the dog vomited and was treated with famotidine (0.5 mg/kg, intravenously [IV], bis in die [BID]; Gaster, Dong-A ST, Seoul, Korea) and maropitant (1 mg/kg, subcutaneously, semel in die [SID]; Cerenia, Zoetis, Seoul, Korea). The rectal temperature decreased to 37.6°C. Respiratory rate increased to 66 breaths/min, and the respirations became shallow. At that time, nasal oxygen therapy was initiated. At 2 hr post-admission, the dog experienced seizures and flumazenil (0.01 mg/kg; Flunil, Bukwang Pharmaceutical, Seoul, Korea) was administered (IV); however, the seizures continued. Therefore, a bolus of diazepam (0.5 mg/kg; Samjin Pharmaceutical, Seoul, Korea) was administered (IV); when the seizures still did not stop, a bolus dose of propofol (2 mg/kg, IV; Provive, Myungmoon Pharmaceutical, Seoul, Korea) was given, at which time the seizures stopped. After 20 min, the dog experienced seizures again and was treated with propofol as a continuous rate infusion (CRI) of 0.2 mg/kg/min. At 3 hr post-admission, urine output was low (0.45 m*l*/kg/hr) and furosemide (1 mg/kg, IV; Handok Pharmaceutical, Seoul, Korea) was administered twice at 30-min intervals. Approximately 5 hr after administration of propofol, the dog was weaned from anesthesia by gradual reductions in the CRI of propofol over the course of 1 hr. After recovering from anesthesia, the seizures did not return. Urine output increased to 1.5 m*l*/kg/hr. Dog 1 remained in a stupor and still presented with severe hematuria; therefore, additional supportive care and monitoring was required. However, the owner decided to transfer the dog to a local hospital, attributable to financial constraints. One day after discharge, we called the owner and it was reported that the dog did not experience further seizures at the local hospital. After being discharged from the local hospital, the hematuria disappeared and the dog was walking and acting normally at home.

In Dog 2, intravenous fluid therapy was instituted using an isotonic crystalloid fluid at 5 m*l*/kg/hr. At 30 min post-admission, the dog experienced seizures. Flumazenil (0.01 mg/kg) was administered intravenously; however, the seizures continued. A bolus dose of propofol (3 mg/kg, IV) was given, and the seizures stopped. However, 30 min after administration of propofol, the dog began experiencing seizures again and was treated with another dose of propofol (1.5 mg/kg, IV). A cuffed endotracheal tube was placed, and oxygen therapy was initiated. Oxygen saturation, as measured by pulse oximetry, was 80%, but improved to 95% with supplementation of oxygen by an endotracheal tube. Flumazenil (0.01 mg/kg, IV) was again administered 1.5 hr post-admission. At 2 hr post-admission, the dog experienced seizures again and was treated with propofol at a CRI of 0.1 mg/kg/min. At 4 hr post-admission, the dog experienced another seizure; therefore, the propofol CRI was increased to 0.2 mg/kg/min. The patient continued to breathe without assistance and did not receive positive pressure ventilation. He became hypothermic under anesthesia; therefore, a forced air heating blanket was provided. Approximately 8 hr after administration of propofol (CRI), the owner decided to transfer the dog to a local hospital, attributable to financial constraints. Therefore, the propofol CRI was gradually reduced. After

recovery from anesthesia, the dog remained in a stupor and still experienced muscle tremors. Its heart rate was 113 beats/min, and the respiratory rate was 30 breaths/min. The pinpoint pupils and PLRs improved, and urine output was 2.7 m*l*/kg/hr at the time of discharge. Two days after discharge, we called the owners to follow-up. The dog was given supportive fluid therapy and the mental status improved at the local hospital. After discharge from the local hospital, the dog was walking and acting normally at home.

Afloqualone is an analogue of methaqualone. Methaqualone is a highly addictive quinazolone derivative with anticonvulsant, sedative-hypnotic, and anxiolytic properties via action on the $GABA_A$ receptor [8]. Because of its extensive history of misuse, the drug has been withdrawn from multiple markets worldwide. Other sedative quinazolone derivatives, such as mecloqualone, cloroqualone, and etaqualone have also been removed from the market, attributable to concerns regarding their potential for overdose and abuse [19]. Afloqualone is not widely used, attributable to photosensitivity and skin irritation issues in human medicine; however, it has seen some popularity in Japan and South Korea [4]. Methaqualone is a depressant that increases GABA receptor activity in the brain and nervous system [8]. An overdose can cause delirium, convulsions, hypertonia, hyperreflexia, vomiting, kidney failure, coma, and death through cardiac or respiratory arrest in humans [13]. GABA receptor agonists intoxication can be a cause of profound coma with brainstem dysfunction mimicking brain death [15]. Paradoxically, hyperaesthesia, hypersalivation, aggressiveness, hyperactivity, hyperthermia and seizure may be observed [3]. Methaqualone poisoning resembles barbiturate poisoning, but with increased motor difficulties and a lower incidence of cardiac or respiratory depression [13, 20]. The disposition and metabolism of afloqualone have been studied in dogs [16]. Afloqualone reaches a peak plasma concentration within 1–2 hr and has a plasma half-life of 7.2 hr in the dog [16]. In the two cases presented here, the owners recognized the first signs of intoxication approximately 1–2 hr after the suspected exposure. According to the National Animal Poison Control Center, the LD_{50} for afloqualone in mice and rats is 397 and 249 mg/kg, respectively. A common dosage of afloqualone for therapeutic use is 60 mg/day in humans. In this report, the dogs ingested approximately 28.6 and 59.6 mg/kg afloqualone in Dog 1 and 2, respectively.

The basic principles for successful treatment for drug intoxications include decontamination if the exposure is recent, monitoring, and symptomatic and supportive therapy [1]. Emesis may be induced in asymptomatic dogs within the first 30 min to 2 hr after ingestion [7]. For animals exhibiting severe depression, emesis is contraindicated because of the risk of aspiration. However, these methods were not considered in these dogs because of the delayed presentation. Activated charcoal should be considered to reduce the amount of afloqualone available for absorption and may have reduced the amount of afloqualone absorbed from the gastrointestinal tract in these dogs, attributable to enterohepatic metabolism of afloqualone; 36.7% of an oral dose is eliminated via the feces in dogs [16]. However, the two dogs in this case series did not receive activated charcoal because of their severe neurologic impairment. Since 51.8% of an oral dose is excreted renally [16], diuresis with IV fluids is recommended; administration of furosemide can be used to force diuresis. Hemoperfusion and hemodialysis have been used for the treatment of GABA agonists poisonings in humans and dogs [18, 23]. In a previous study, dogs were experimentally given large doses of barbiturates, methaqualone and ethanol and were treated by hemoperfusion using a column packed with charcoal coated with an acrylic hydrogel. [22]. Clearances for these drugs were significantly higher than those reported for hemodialysis.

The use of barbiturates for seizure control is not recommended because this class of drugs may cause more profound CNS depression [1, 7]. Despite also being a GABA agonist, diazepam was administered to control seizures based on anecdotal experience of limited adverse effects [10, 12]. Uncontrolled seizures may be treated with propofol or isoflurane; however, exacerbation of respiratory depression may result [12].

In Dog 1, the dog had severe hematuria. Urinary tract bleeding has been reported as a sign of overdose or side effect of methaqualone [6]. In the synthesis of methaqualone, two organic compounds, ortho-amino benzoic acid and ortho-toluidine 2 amino-toluene, are present. Ortho-amino benzoic acid does not cause hematuria, whereas ortho-toluidine may cause hematuria [6]. Afloqualone also contains ortho-toluidine, which may have contributed to the hematuria observed in this dog [17].

Flumazenil is an imidazobenzodiazepine that is a competitive antagonist acting on CNS benzodiazepine receptors and is well known for its role as a reversal agent for diazepam and other GABA agonists [12]. Further, flumazenil is known as a potential antidote for other non-benzodiazepine GABA agonists [12, 21]. Therefore, we used flumazenil as an antagonist of afloqualone in these cases; however, it was ineffective. Flumazenil has been shown to effectively antagonize diazepam-induced decreases in cGMP, but does not affect the cGMP-decreasing effects of ethanol, phenobarbital, methaqualone, haloperidol, etazolate, meprobamate, and muscinol in humans [21]. While afloqualone intoxication in dogs has not been previously reported in the veterinary literature, intoxication with baclofen, another centrally acting muscle relaxant, has been reported [9, 10, 18]. Baclofen is a GABA analogue that interacts with GABA receptors and causes similar clinical signs as seen in the case studies reported here, including seizure and respiratory depression. Reports are conflicting regarding the efficacy of flumazenil as a reversal agent for baclofen [9].

Optimal management and follow-up of these cases were limited, attributable to financial constraints of the owners. However, upon follow-ups with phone calls, the owners reported that the dogs in these case reports had recovered via symptomatic and supportive therapies. This is the first documented report of afloqualone poisoning in dogs and provides an example of a successful therapy that could be employed to ensure a good prognosis in other similar cases.

ACKNOWLEDGMENTS. This work was supported by the BK21 plus program for Veterinary Science Research and Research Institute for Veterinary Science, College of Veterinary Medicine, Seoul National University.

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