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Topical Review

Adderall® (Amphetamine-Dextroamphetamine) Toxicity

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A B S T R A C T

The American Psychiatric Association estimates that 3–7% of US school–aged children exhibit attention-deficit/hyperactivity disorder (ADHD). Adderall® (amphetamine dextroamphetamine) and a variety of brand names and generic versions of this combination are available by prescription to treat ADHD and narcolepsy. Both immediate and sustained release products are used as are single agent amphetamine medication. Knowing the exact agent ingested can provide information of dose labeled and length of clinical effects. These drugs are used off label by college students for memory enhancement, test taking ability, and for study marathons. These agents are DEA Schedule II controlled substances with high potential for abuse. For humans with ADHD or narcolepsy, standard recommended dosage is 5–60 mg daily. Amphetamine and its analogues stimulate the release of norepinephrine affecting both α– and β–adrenergic receptor sites. α–Adrenergic stimulation causes vasoconstriction and an increase in total peripheral resistance. β-Adrenergic receptor stimulation leads to an increase in heart rate, stroke volume, and skeletal muscle blood flow. Clinical signs of Adderall® overdose in humans and dogs include hyperactivity, hyperthermia, tachycardia, tachypnea, mydriasis, tremors, and seizures. In addition, Adderall intoxication in dogs has been reported to cause hyperthermia, hypoglycemia, hypersegmentation of neutrophils, and mild thrombocytopenia. Diagnosis can be confirmed by detecting amphetamine in stomach contents or vomitus, or by positive results obtained in urine tests for illicit drugs. Treatment is directed at controlling life-threatening central nervous system and cardiovascular signs. Seizures can be controlled with benzodiazepines, phenothiazines, pentobarbital, and propofol. Cardiac tachyarrhythmias can be managed with a β-blocker such as propranolol. Intravenous fluids counter the hyperthermia, assist in maintenance of renal function, and help promote the elimination of amphetamine and its analogues. Prognosis after poisoning with Adderall® depends upon the severity and duration of clinical signs at presentation. Differential diagnoses that should be considered in cases of suspected amphetamine overdose are any other agents that can cause central nervous system stimulation, tremors, and seizures. This article discusses our present understanding of Adderall® intoxication and examines 3 dogs presented to our practice after ingestion of large amounts of the drug.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is the most commonly diagnosed neurobehavioral disorder affecting between 3% and 7% of school–aged children.[1] This disorder results in delayed learning ability, impaired academic achievement, and delayed maturation. Symptoms include having trouble in concentrating or completing simple or complex tasks, losing or misplacing important items, forgetfulness, being easily distracted, hyperactivity, restlessness, impulsive behavior, inability to get along with others, and frequent insubordination. Once thought to regress largely in adolescence, a growing body of work suggests that ADHD and associated disorders persist into adulthood in the majority of cases.[2] If left untreated, this disorder robs many young people of their potential and makes it difficult for them to be successful. Only a trained psychologist, psychiatrist, or physician can make a diagnosis of ADHD with certainty based upon past behavior, medical testing, and clinical observations. Adderall® (amphetamine and dextroamphetamine salts) is a drug used in treating ADHD and narcolepsy.[3] The standard daily dose in humans is 2.5–60 mg daily given 1–3 times.[4] Adderall® is available as a tablet in 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg, 20 mg, and 30 mg strengths. It is also available in an extended–release (XR) form as a 15–mg tablet. It is a controlled substance available only by prescription from a licensed physician and, like other amphetamines, is a schedule II drug with a high potential for abuse. In addition to the prescription use of the drug, recently Adderall® has been seen to be abused by college students and young people, both as a study aid during examinations and as a recreational drug.[1,4,5] Recently, we have seen 3 dogs present for accidental ingestion of Adderall®. In this discussion, we examine Adderall® overdose in companion animals.

Sources

Amphetamine is the parent compound (α–methylphenylethylamine) and belongs to the family of phenylethylamines. Numerous substitutions of the phenylethylamine backbone are possible, and all these spin–off, amphetamine–like compounds are referred to as amphetamine analogues. Currently, in human medicine, there are very few legitimate medical indications for amphetamine, although it is still used to treat ADHD and narcolepsy, and for short–term weight–reduction therapy. Amphetamine itself is no longer used in veterinary medicine.[6] Prior to the enactment of the Controlled Substance Act of 1970, amphetamine was used in veterinary medicine as a central nervous system (CNS) and respiratory stimulant to overcome the depressive effects of barbiturates in dogs. Today, nearly all the amphetamine exposures seen by veterinarians are by accidental ingestions of prescription drugs. Occasionally, because of the resurgence of amphetamine abuse by people, animals are seen after ingesting street forms such as methamphetamine and methylenedioxymethamphetamine (MDMA or "ecstasy"). Currently, methamphetamine, along with its various

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analogues, is the most common illicit drug produced by clandestine laboratories in the United States. Owing to the ease and relative low cost of methamphetamine production, cost to the user for methamphetamine is less than one–third the price of cocaine. In addition, methamphetamine has a much longer half–life than cocaine QJ;(12 hours compared with 90 minutes) and, therefore, a much longer duration of action.[7] Both its low cost and prolonged activity contribute to the popularity of methamphetamine and its analogues. Recently, the productions of "bath salts," synthetic designer drugs, have also received some notoriety in the press. These products can contain 4-methylmethcathinone (mephedrone) that transforms to cathinone (benzylketoamphetamine), which is thought to be the primary active agent and produces the potency and clinical signs of methcathinone (comparable to that of methamphetamine).[8] Small-animal clinicians must make every effort to keep current with regard to both prescription and illicit drugs and their various effects if they are to provide effective treatment.

Toxic Dose

In dogs, the oral median lethal dose for amphetamine can be anywhere from 9-11 mg/kg for methamphetamine hydrochloride to 20-27 mg/kg for amphetamine sulfate.[9] The intravenous median lethal dose for amphetamine in dogs is 5.85 mg/kg.[10] In humans, death from amphetamine has been recorded with as low a dose as 1.5 mg/kg.[11] In rats, the oral LD_{50} for dextroamphetamine is 96.8 mg/kg.

Toxicokinetics and Mechanism of Toxicity

Pharmacologic effects of amphetamine are complex and diverse but their primary mechanism of action is the release of catecholamines, primarily dopamine and norepinephrine from presynaptic terminals.[12] Amphetamine and its analogues work indirectly to cause neuronal stimulation by increasing postsynaptic catecholamines. This occurs via their blocking of presynaptic uptake activity, by blocking presynaptic vesicular storage, and by reducing cytoplastic destruction of catecholamines through inhibition of mitochondrial monoamine oxidase.[13] Amphetamines lack the local anesthetic effects on cardiac and nervous tissue that occur with cocaine.[7]

Although a number of receptors have been implicated in mediating the complex physiological response to amphetamine, the underlying clinical effects associated with amphetamine overdose involve excessive stimulation of the sympathetic nervous system. The rapid and sustained activation of the sympathetic nervous system is responsible for amphetamine's signature of tachycardia, hypertension, mydriasis, diaphoresis, and psychomotor agitation.[14] Furthermore, the prolonged release of central monoamines and activation of the sympathetic nervous system are responsible for most of the acute recognizable neurologic complications associated with amphetamine intoxication (hyperthermia, agitation, and seizures).

The increased norepinephrine causes sympathetic nervous stimulation. This results in bronchodilation, hyperglycemia, and increases in heart rate, cardiac output, blood pressure, and pupil size, all of which are effects noted in the "fight-or-flight" response.[15] CNS effects of amphetamine appear to be mediated primarily by dopaminergic alterations affecting changes in mood, excitation, motor movements, and appetite. The most identifiable effects of amphetamines are those caused by catecholamine release and resultant stimulation of peripheral α- and β-adrenergic receptors. In the CNS, increased norepinephrine at the locus caeruleus mediates the anorectic and alerting effects, and also some locomotor stimulation. The increase in central dopamine mediates stereotypical behavior and some of the other locomotor activities.

Amphetamines are highly lipid soluble and are readily absorbed across most biological membranes. Tissue redistribution of amphetamine is extensive and high lipid solubility leads to increased concentration relative to serum in the liver, kidneys, and lung.[15] After oral ingestion, peak plasma concentrations occur within 2-3 hours.[6] Amphetamines undergo some hepatic metabolism and both the unchanged forms and the metabolites of the drug and its analogues are excreted into the urine. Some of the metabolites are pharmacologically active. Generally, metabolism is minimal and most amphetamines are excreted as the parent molecule. The majority of amphetamines are eliminated in the urine. The serum half-lives of amphetamine and its analogue compounds are urine pH dependent and range between 7 and 34 hours.[16] The more acidic the urine, the shorter the half-life because of reduced renal reabsorption of ionized urinary amphetamine.[15] As much as 30% of amphetamine is excreted in the urine unchanged.

Amphetamines have been shown not only to cause seizures but also to induce stereotyped repetitive movements in both humans and animals.[14,17,18,19] Non–goal directed repetitive behaviors like circling, head bobbing, facial tics, licking, lip smacking, foot paddling, and sniffling have been described in a variety of animals that were given amphetamines.[17] These signs disappear while they are sleeping. With time, treatment, and cessation of amphetamine use, these signs resolve. Although the neurologic mechanism behind this repetitive stereotypic behavior is not well understood, it appears to involve dopamine.[14] Increases in stereotypic locomotor activities (circling, etc.) and, recently, dopamine-mediated decreases in acetylcholine have been implicated.[14,17]

Clinical Signs

Onset of clinical signs of amphetamine toxicity can vary with the formulation of the product ingested. Signs may be seen almost immediately or can be delayed for several hours with ingestion of XR formulations. Amphetamines act through causing neuronal stimulation by increasing postsynaptic catecholamines (norepinephrine and dopamine). An increase in postsynaptic norepinephrine causes stimulation of the sympathetic nervous system.[15] Release of norepinephrine stimulates both α- and β-adrenergic receptor sites.[12] Bronchodilation and increases in heart rate, cardiac output, and blood pressure all occur as a result. Recently, myocardial infarction has been reported after ingestion of Adderall®.[20] In addition, Adderall® XR was temporarily taken off the market in Canada due to increases in cardiac-related diseases.[20] Animals and humans also exhibit mydriasis, hypersalivation, hyperthermia, and tachycardia.[6] The CNS effects of amphetamine are thought to be mediated primarily by dopaminergic alterations and include ataxia, excitation, and changes in motor movements, vocalizations, tremors, and seizures.[15] In addition, repetitive stereotypic motions may be observed.[14,18] Table 1 summarizes the most common clinical signs observed in instances of amphetamine intoxication.

Table 1
Clinical signs of amphetamine intoxication

- Hyperactivity
- Hypersalivation
- Hyperthermia
- Mydriasis
- Tremors
- Hypoglycemia
- Tachycardia
- Increased blood pressure
- Ataxia
- Seizures
- Repetitive stereotypical behaviors

Table 2
A minimum database for amphetamine intoxication

- Complete blood count
- Biochemical profile
- Coagulation panel
- Blood gas evaluation to determine acid-base status (if available)
- Blood pressure
- Electrocardiogram
- Body temperature check for hyperthermia
- Seizure watch

Minimum Database

Minimum database in cases of amphetamine poisoning should include a complete blood count, a biochemical profile, a coagulation panel, an electrocardiogram (ECG), and a blood pressure analysis. A blood gas evaluation to determine acid-base status should be run, if possible. A urinalysis should be performed to monitor myoglobinuria. Animals should be closely observed for hyperthermia and seizures. A summary of a minimum database necessary to evaluate an animal following real or suspected amphetamine toxicity is included in Table 2.

Diagnostics and Confirming Tests

Amphetamines can be identified in vomitus, stomach contents, and urine by human toxicologic laboratories. A good relationship with the toxicology section of a local human hospital or a local human toxicologist can have many benefits. Consultation with a diagnostic toxicologist should always be sought before collection and submission to prevent nondiagnostic samplings and to improve accuracy. In addition to local hospitals, regional veterinary teaching hospitals and poison centers can likewise be very helpful. Amphetamines would test positive (+) on human amphetamine or methamphetamine urine tests, but these screening tests have not been validated for use in animals. Other ways that can help confirm amphetamine poisoning but are not diagnostic are as follows: (a) sinus tachycardia and ventricular arrhythmias on ECG, (b) metabolic acidosis confirmed by blood gas analysis, (c) an increase in blood pressure (hypertension), (d) myoglobinuria secondary to rhabdomyolysis identified by urinalysis, and (e) hyperthermia.

Finally, as in other animals suffering from hyperpyrexia, the blood may reflect heat-induced damage of erythrocytes, neutrophils, and platelets.[21,22] Such hematologic changes associated with Adderall toxicity in a dog have been described (metarubricytosis, hypersegmentation and pyknosis of neutrophils, and thrombocytopenia).[4] However, these changes were not consistent in every dog presented to our hospital for dextroamphetamine ingestion. A list of diagnostic and confirming tests to aid in establishing definite amphetamine toxicity are shown in Table 3.

Treatment

Just as in any poisoning, initiation of treatment must not supersede the essentials of emergency medicine. Temperature, respiration, heart rate and rhythm must all be strictly monitored and never overlooked. The mainstays of treatment for amphetamine-poisoned animals are supportive care, control of behavior, management of arrhythmias, stopping seizures, and temperature reduction. There remains no specific antidote for amphetamine intoxication. Hyperthermia, a frequent manifestation of this poisoning syndrome, must be swiftly managed with immediate intervention. Animals seen early enough, within 30 minutes of ingestion and showing no signs, can be treated by emesis and administration of activated charcoal. The efficacy of the use of activated charcoal in treating amphetamine exposure has been well documented in mice; sustained or XR forms of the drug may require repeated doses of activated charcoal.

Seizures can be successfully treated using benzodiazepines, barbiturates, or propofol. Although benzodiazepines have been reported to exacerbate the neurologic effects of amphetamine,[6,24] these developments have not been seen with diazepam use at our hospital. Chlorpromazine (given intravenously at 10-18 mg/kg) prevented lethal effects from amphetamine in experimentally dosed dogs and is also recommended for controlling CNS excitation and seizures owing to its dopamine excitatory receptor antagonist properties.[23] Acepromazine (given intravenously at 0.05 mg/kg) has also been recommended. The phenothiazines are also used to manage the agitation, but they must be utilized recognizing that they may lower seizure threshold. The serotonin antagonist cyproheptadine has also been suggested to combat agitation. Dosage recommended is 1.1 mg/kg given orally in dogs and 2-4 mg total dosage per cat. Hyperthermia should be dealt with early and corrected using intravenous fluids, fans, ice packs, or cool-water baths. Animals must be continually monitored to identify subsequent hypothermia. Intravenous fluids are necessary not only to regulate body temperature but also to maintain renal function, protect the kidneys from myoglobinuria, and to promote elimination of amphetamines. Although urinary acidification can significantly increase the elimination and decrease the half-lives of amphetamine and its analogues, this pH manipulation does not decrease toxicity and may increase the risk of renal compromise and acute tubular necrosis from rhabdomyolysis by precipitating ferrihemate in the renal tubules. Urinary acidification using ascorbic acid (20-30 mg/kg PO) or ammonium chloride (100-200 mg/kg PO divided QID) has been shown to increase the elimination of amphetamine in a variety of species but this procedure is contraindicated if the animal's acid-base status cannot be monitored or if myoglobinuria is already present.[6] The intense muscle activity caused by tremors and seizures can result in metabolic acidosis and rhabdomyolysis. Fluid therapy, but not urine acidification, should be employed to treat these animals.

Table 3
Diagnostics and confirmatory test for amphetamine poisoning

(a) Detection of amphetamines in vomitus, stomach contents, or urine by human toxicologic laboratories
(b) Illicit drug urine test (human): animals may test positive on amphetamine or methamphetamine tests—however, these tests are not validated yet for animal use
(c) Hyperthermia
(d) Sinus tachycardia and ventricular arrhythmia—electrocardiogram
(e) Hypertension found on blood pressure check
(f) Metabolic acidosis on blood gas test
(g) Myoglobinuria on urinalysis
(h) Metarubricytosis, thrombocytopenia, and pyknosis and hypersegmentation of neutrophils (fever induced)
(i) Hypoglycemia

Table 4
Management of animals with amphetamine toxicity

Gastric decontamination
- If brought in within 30 min of ingestion, induce emesis
  Apomorphine (dogs): 0.04 mg/kg IV
- If animal is alert, start activated charcoal therapy
  Extended-release formulations may require repeated doses

Agitation
- Phenothiazines: acepromazine (0.05 mg/kg IV)
  Chlorpromazine (0.5 mg/kg IV)
- Cyproheptadine: serotonin antagonist
  Dogs—1.1 mg/kg PO
  Cats—24 mg per cat total

Tachycardia–tachyarrhythmias
- Propranolol (0.020.06 mg/kg IV)—β-blocker
- Tremors
- Methocarbamol (50100 mg/kg IV)

Seizures
- Phenobarbital (34 mg/kg IV to effect)
- Inhalant anesthetics (isoflurane and sevoflurane)
- Propofol CRI
- Diazepam (0.25–0.5 mg/kg IV to effect)

Hyperthermia
- Intravenous fluids
- Fans
- Ice packs
- Cool baths
- Chemical sedation
- Monitor continually to avoid hypothermia

CRI, continuous rate infusion.

Tachyarrhythmias and tachycardia can be controlled with β-blockers such as propranolol (0.02-0.06 mg/kg given intravenously) or metoprolol (0.1 mg/kg PO). Ventricular dysrhythmias should be treated with lidocaine (0.025-0.08 mg/kg/min infusion). Tremors can be managed with methocarbamol (50-100 mg/kg given intravenously). Seizure activity can be treated by benzodiazepines (diazepam 0.25–0.5 mg/kg given intravenously) or by barbiturates given to effect (phenobarbital 3-4 mg/kg given intravenously). Animals must be kept quiet and sensory stimulation should be kept to a minimum. Intractable seizures can be managed with inhalant anesthetics (isoflurane and sevoflurane) or on a propofol continuous rate infusion. Sedation prevents further muscle contraction, stops tremors and seizures, and thereby lowers heat production. In conclusion, recently, intravenous lipid therapy has been considered for use with regard to the more lipophilic amphetamine analogue compounds.[6] Table 4 summarizes therapeutic treatment to an animal suffering from amphetamine toxicity.

Discussion

Adderall® (amphetamine salts and dextroamphetamine salts) is a prescription drug commonly prescribed for children with ADHD. Currently, it is estimated that between 3% and 7% of school-aged children in the United States have some degree of ADHD. In addition, Adderall® is becoming more commonly abused by young people and college students with nonprescription use. The drug is widely prescribed, found in a surprising percentage of American homes, and has a high potential for abuse. The greater availability and use of this drug increases the chances for inadvertent animal exposure. Recently, we saw 3 dogs present to our emergency room that had ingested large amounts of Adderall®.

In the last 12 months, 3 dogs presented to our practice after ingesting various amounts of Adderall®. Dog 1 was a 7-year-old, spayed female border collie (21 kg) that had consumed 20 20–mg tablets at an unknown amount of time before admission to our emergency room. This amounted to 400 mg ingested or approximately 10 mg/kg body weight. Upon presentation, the dog was recumbent, had bilaterally dilated pupils, was tremoring, and had 2 short seizures on the way to the hospital. The dog had a rectal temperature of 41°C. When aroused, the dog would repeatedly circle to the right and bring the right front paw across the muzzle repetitively.

Dog 2 was a 4.5-year-old, neutered male Jack Russell terrier (11 kg) that had consumed 12 15–mg Adderall® XR (extended release) tablets 2 hours before admission. This would represent 180 mg ingested or 17 mg/kg body weight. At presentation, the dog was alert, responsive but agitated, had bilaterally dilated pupils but showed no tremors or seizures. Rectal temperature was 42°C. Once in a cage, the dog continually circled, would not lie down, and was restless.

Dog 3 was a 5-year-old, spayed female shepherd-cross (33 kg) that had consumed 25-30 20–mg Adderall® tablets 1 hour before admission. This represented approximately 600 mg ingested or nearly 18 mg/kg body weight. At the time of admission, the dog was alert and responsive but extremely agitated and revealed a rectal temperature of 41.5°C. The dog had bilaterally dilated pupils. The dog was given apomorphine (0.04 mg/kg IV) to induce emesis but did not vomit. Two hours after admission to our intensive care unit, the dog became recumbent, started to tremor, and had 1 short (60 second) seizure. Postictally, the dog displayed the stereotypical repetitive behavior (circling and repeated paw lifting) that Dog 1 also manifested. The normal daily dosage for Adderall® in humans with ADHD or narcolepsy varies from 5-60 mg. The dogs in our study ingested from 3-10 times the highest daily dosage prescribed for humans.

Upon presentation to our hospital, all 3 dogs were given thorough physical exams, had body temperature, mentation, and heart rate rhythm assessed. Next blood samples were drawn for a CBC and a biochemical profile panel. All had electrocardiograms run. After the blood samples were taken, intravenous catheters were put in and all 3 of the dogs were started on 0.9% normal saline to counter their hyperthermia and to support kidney function. All 3 were started on phenobarbital (3 mg/kg IV) and methocarbamol (50 mg/kg IV) to control tremors and seizures, supported with intravenous fluids, and were regularly monitored for status of body temperature.

The ECGs in all 3 dogs revealed tachycardia (dog 1: 180 beats/min, dog 2: 180 beats/min, and dog 3: 192 beats/min) but no premature ventricular contractions or other arrhythmias. After 8 hours of intravenous fluids, the fever in all 3 dogs resolved (dog 1: 37.0°C, dog 2: 37.5°C, and dog 3: 37.3°C). Upon administration of the phenobarbital, the tremors, seizures, and stereotypical repetitive behaviors all ceased. No more seizures were observed and by the second day after presentation, all the neurologic signs (circling, repetitive motions) had resolved. All 3 dogs were clinically normal (no fever, no pupillary dilation, no tremors, no seizures, and no repetitive motion behaviors, and were eating and drinking) when they were released on the third day of hospitalization. The dogs were sent home on no medication.

The results of the complete blood count for the 3 dogs revealed no anemia and a normal white blood cell count. All 3 dogs showed elevated lactate levels at presentation that resolved

Table 5
CBC results from 3 dogs with Adderall® toxicity upon admission

Value	Dog 1	Dog 2	Dog 3	Range*
WBC/μL	6350	6100	7200	6000–17,000
Segmented neutrophils/μL	5000	4600	5600	3000–11,000
Lymphocytes/μL	1100	1105	1240	1000–5000
Monocytes/μL	160	190	150	150–1250
Eosinophils/μL	100	110	105	100–1250
RBC (M/μL)	5.66	5.8	6.0	5.5–8.5
Hemoglobin (g/dL)	14.3	15.5	16.2	10–20
ACT (%)	41	39	43	37–55
MCV (fL)	75.4	76.2	76.0	60–72
MCHC (g/dL)	33.5	33.0	32.5	32–36

CBC, complete blood count; WBC, white blood cell; RBC, red blood cell; MCV, mean cell volume; MCHC, mean cell hemoglobin concentration.

* Reference range taken from Antech Clinical Pathology Laboratory.

with fluid therapy. The 3 dogs shared a mild hypoglycemia: dog 1 (60 mg/dL); dog 2 (64 mg/dL); and dog 3 (58 mg/dL). Hypoglycemia has been previously reported in several different instances of hyperthermia. The hypoglycemia in these cases may have resulted from increased glucose utilization owing to the tremors and seizures, increased glucose utilization owing to the increased catecholamine release, decreased glucose production owing to mild liver dysfunction due to increased metabolism, or a generalized increase in adenosine triphosphate demand combined with the high body temperature. In a previous report of Adderall® toxicity in a dog, the blood work revealed mild hypoglycemia, mild thrombocytopenia, hypersegmented neutrophils, and several pylenotic nuclei.[4] Also in that previous report, the dog showed coagulation abnormalities that, together with the described thrombocytopenia, might predispose animals ingesting large amounts of Adderall® to the development of disseminated intravascular coagulation. This is probably the result of hyperthermia. Thrombocytopenia and coagulation abnormalities are commonly seen in dogs with fever and heat-induced illnesses.[20-22] Disseminated intravascular coagulation is believed to occur in heat stroke as a result of heat-induced damage to endothelial cells with subsequent activation of platelets and the coagulation cascade. The results of blood work for the dogs in our study are included in Tables 5 and 6.

Table 6
Biochemical panel on 3 dogs with Adderall® toxicity at presentation

Value	Dog 1	Dog 2	Dog 3	Range*
Glucose (mg/dL)	60	64	58	60–135
Albumin (g/dL)	2.7	2.9	3.1	2.4–3.6
Alanine aminotransferase (μ/L)	100	98	110	10–130
Alkaline phosphatase (μ/L)	148	135	130	24–150
Glutamyl transferase (μ/L)	12	17	10	0–25
BUN (mg/dL)	20	19	15	5–30
Creatinine (mg/dL)	1	1.2	1.1	0.3–1.2
Phosphorus (mg/dL)	5.4	4.5	4.0	2.9–6.2
Magnesium (mg/dL)	1.9	1.7	1.8	1.7–2.1
Calcium (mg/dL)	11.2	9.8	10.2	9.3–11.8
Cholesterol (mg/dL)	200	232	240	120–250
Total protein (g/dL)	6.4	5.9	6.0	5.7–7.8
Globulin (g/dL)	1.9	2.4	2.3	1.7–3.8
Total bilirubin (mg/dL)	0.2	0.4	0.1	0–0.9
Sodium (mmol/L)	145	142	140	139–147
Potassium (mmol/L)	3.6	3.4	3.3	3.3–4.6
Chloride (mmol/L)	114	110	116	107–116
Lactate (mg/dL)	16	14	15	2–13

BUN, blood urea nitrogen.

* Reference range taken from Antech Clinical Pathology Laboratory.

Table 7
A partial list of differential diagnoses in amphetamine toxicosis*

- Methylxanthines
- Ma huang
- Ephedra
- Guarana root
- Permethrin (cats)
- Lead
- 4-aminopyridine
- 5-fluorouracil
- Pseudoephedrine
- Metaldehyde
- Tremorgenic mushrooms
- Strychnine
- Tricyclic antidepressants
- Organophosphates (insecticides)
- Carbamates (insecticides)
- Sodium ion toxicosis
- Organochlorine insecticides

* Any agent that can cause CNS stimulation.

Prognosis and Prevention

Prognosis for Adderall® ingestion is similar for other amphetamines and depends upon severity and duration of clinical signs. Trauma, hypoxia, hyperthermia, or even cerebral edema can result from myoglobinuria. If the animal survives the initial physiological changes and biochemical abnormalities, and if the CNS, cardiac signs, and kidney problems are swiftly addressed, the prognosis for a full recovery is good. For most dogs managed aggressively (fluids and seizure control) few permanent problems should be expected. Although the clinical signs of this toxicity are dramatic, most animals show no long-term clinical consequences of Adderall® toxicity.

Prevention of accidental Adderall® intoxication in dogs (or for that matter any drug) depends upon responsible storage of all medications. Both human and animal medications should be stored in drug cabinets with a working latch. No drugs should be kept on night stands next to beds. All old human medication should be accounted for, returned to the pharmacy, and incinerated. They should never be thrown into garbage cans or flushed down the toilet. Some pharmacies charge for this incineration service but it is worth not having animals or children blunder across dangerous drugs or having toxic molecules enter our water supply. Periodically, the DEA hosts medication take back days. Information about programs in your area can be found at http://www.deadiversion.usdoi.gov/drugdisposal/index.html or call the national poison hotline at 800-222-1222. These simple measures can be life saving and prevent discarded drugs from contaminating our environment.

Gross and Histologic Lesions

Despite the severity of clinical signs in dogs following Adderall® ingestion (which can be quite severe), if no kidney problems develop as a result of the poisoning, there are no specific or pathognomic histopathologic lesions consistent with this intoxication.[24]

Differential Diagnoses

Any agent that can cause CNS stimulation, tremors, and seizures must be included in a differential diagnosis list for Adderall® toxicosis. These would include a host of substances such as methylxanthines, metaldehyde, tremorgenic mycotoxins, pseudoephedrine, strychnine, tricyclic antidepressants, 5-fluorouracil, organochlorine insecticides, organophosphates and carbamate insecticides, nicotine, 4-aminopyridines, sodium ion toxicosis, lead, serotonergic medications, and herbal preparations containing ma huang, guarana root, or ephedra.[6] Molecules like

these must all be considered before arriving at a particular suspect for the poisoning. A partial list of differential diagnoses for amphetamine toxicosis is included in Table 7.

To arrive at a correct toxicologic diagnosis, the clinicians must assemble a coherent picture based upon history, clinical signs, laboratory results, and appropriate response to therapy. Animals ingesting toxic substances remain among the most challenging cases faced by small-animal clinicians. Nevertheless, through the judicious use of available resources (local toxicology laboratories, local hospitals, regional poison centers, local toxicologists, regional veterinary colleges, the national poison hotline (800-222-1222), the national animal poisoning hotline (888-426-4435), and an awareness of the current literature and treatment protocols), many seemingly devastating poisonings can have very favorable outcomes.

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