

PEER-REVIEWED

Allium species poisoning in dogs and cats

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Wild and domesticated *Allium* species have been used for culinary and ethnomedicinal purposes since the beginning of recorded history. About 95 species of native or cultivated leeks, chives, garlic, shallots, scallions, and onions are present in North America, and more than 80 ornamental *Allium* species are available. All *Allium* species and the products derived from them can be toxic to dogs and cats¹; however, relatively few *Allium* species are of important toxicologic interest.

Table 1 lists the *Allium* species native to North America that are most commonly involved in animal poisonings.¹ The

Onions, leeks, garlic, and chives are commonly involved in toxicosis in dogs and cats.

domesticated species commonly involved in toxicosis include *Allium cepa* (onion), *Allium porrum* (leek), *Allium sativum* (garlic), and *Allium schoenoprasum* (chive). The plants form solitary or clustered bulbs and are strongly aromatic, with an onion or garlic odor when crushed. The distinctive aroma distinguishes *Allium* species from morphologically similar poisonous plants, particularly death camas (*Zigadenus* species).¹

Toxicity

Allium species contain a wide variety of organosulfoxides, particularly alk(en)ylcysteine sulfoxides. Trauma to the plants, such as chewing, converts the organosulfoxides to a complex mixture of sulfur-containing organic compounds. Many of these compounds or their metabolites are responsible for the odors, flavors, and pharmacologic effects of these plants. Many *Allium* species' organosulfur compounds appear to be readily absorbed through the gastrointestinal tract and are metabolized to highly reactive oxidants.² Cooking or spoilage of *Allium* species does not reduce their potential toxicity.¹

Mechanism of action

The primary toxicologic mechanism of *Allium* species-derived organosulfur compounds is oxidative hemolysis, which occurs when the concentration of oxidants in the erythrocyte exceeds the capacity of the antioxidant metabolic pathways. Catalase

antioxidant activity in erythrocytes in dogs is low,³ and normal hemoglobin in cats is about two to three times more susceptible to oxidative damage than the hemoglobin in other species.⁴

Oxidation of the exposed beta-93 cysteine residues present in hemoglobin results in the formation of sulfhemoglobin.⁵ Sulfhemoglobin is less soluble than hemoglobin, so it precipitates, aggregates, and binds to the cell membrane and forms Heinz bodies. Other types of oxidation of hemoglobin globin chains result in membrane cross-linking reactions and eccentrocyte formation.⁶ The formation of Heinz bodies and eccentrocytes increases erythrocyte fragility and extravascular

hemolysis. Direct oxidative damage to the erythrocyte cell membrane and its sodium-potassium pump or the oxidative production of hemin also contributes to cell lysis. Oxidation of the heme ion and associated methemoglobinemia results in a left shift of the hemoglobin-oxygen dissociation curve, decreased blood oxygen transportation capacity, and, ultimately, impaired delivery of oxygen to the tissues.

Thus, the result of the oxidative hemolytic process induced by *Allium* species consumption is the onset of anemia, methemoglobinemia, and impaired oxygen transportation. Although marked Heinz body formation may be present within a day after onions are ingested, the anemic nadir typically develops several days later.

Allicin and ajoene, pharmacologically active agents in garlic, are potent cardiac and smooth muscle relaxants, vasodilators, and hypotensive agents.⁷⁻⁹ Also, ajoene and other organosulfur compounds derived from onions are potent antithrombotic agents.¹⁰ Thus, hypotensive and antithrombotic effects can exacerbate the physiologic effects of anemia and impaired oxygen transportation. Garlic preparations that have not been aged cause direct damage to the gastric and ileal mucosa, resulting in pain and diarrhea.¹¹

Exposure and susceptibility

Allium species toxicosis most commonly occurs after oral consumption. In addition to consuming fresh plant material,

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TABLE 1 *Allium* Species Native to North America Most Commonly Involved in Animal Toxicosis

Scientific Name	Common Name	Appearance*	Distribution*
<i>Allium canadense</i>	Meadow garlic		
<i>Allium cernuum</i>	Nodding onion		
<i>Allium validum</i>	Pacific onion		
<i>Allium vineale</i>	Wild garlic		

*Photographs and distribution maps are reproduced with permission from: The PLANTS Database, Version 3.5 (<http://plants.usda.gov>). National Plant Data Center, USDA, NRCS. 2004. Baton Rouge, LA 70874-4490. Photo credits: *A. canadense* and *A. cernuum*, T.G. Barnes; *A. validum*, B. Moseley; *A. vineale*, J. Stasz.

consuming juice, fresh and aged dietary supplements, powdered cooking preparations, dehydrated material, or food preparations derived from or containing *Allium* species can be potentially toxic to dogs and cats.¹ *Allium* species toxicosis typically ensues after consumption of a single large quantity of the material or repeated small amounts. Dogs and cats are highly susceptible to onion toxicosis: Consumption of as little as 5 g/kg of onions in cats or 15 to 30 g/kg in dogs has resulted in clinically important hematologic changes. Onion toxicosis is consistently noted in animals that ingest more than 0.5% of their body weight in onions at one time.

Dogs with heritable high erythrocyte reduced glutathione and potassium concentrations are more susceptible

In severely affected animals, a blood transfusion and supplemental oxygen therapy may be required.

to the hematologic effects of onions.¹² This trait is relatively common in Japanese breeds. Other inborn errors in metabolism or nutritional deficiencies that result in decreased erythrocyte antioxidant defenses, such as glucose-6-phosphate dehydrogenase deficiency or zinc deficiency, could increase an animal's susceptibility to *Allium* species toxicity.¹³ Concurrent treatment with xenobiotics, drugs, or dietary factors that induce erythrocyte oxidative injury (e.g. propofol, propylene glycol, dl-methionine, sulfonamides, sulfapyridine, large doses of vitamin K₃, benzocaine) or diminish erythrocyte oxidative defenses (e.g. acetaminophen) is likely to increase an animal's susceptibility to *Allium* species toxicosis.

Clinical signs and laboratory findings

In dogs and cats, clinical signs of *Allium* species toxicosis may appear within one day of consumption if large amounts of material have been ingested; however, it is more common for clinical signs to develop after a lag of several days. Clinical signs often include depression, hemoglobinuria, hemoglobin and possibly hemosiderin urinary casts, icterus, tachypnea, tachycardia, weakness, exercise intolerance, and cold sensitivity. Inappetence, abdominal pain, and diarrhea may also be present. In cases of recent ingestion, the affected dog's or cat's breath may smell of onions or garlic.

Clinical pathology findings are consistent with intravas-

cular and extravascular hemolysis, Heinz body anemia, ecthrocytosis, hemoglobinemia, hemoglobinuria, hyperbilirubinemia, methemoglobinemia, and, if the animal survives long enough, an accompanying regenerative response.¹

Necropsy and histologic findings typically indicate hemolytic anemia. Because of the common lag of several days between ingestion and the development of clinical signs, gastrointestinal erosion or *Allium* species in the gut content may not be seen. Histopathologic findings, although consistent with hemolytic anemia, are not specific for *Allium* species toxicosis and may include deposition of hemosiderin in the phagocytic cells of the liver, spleen, and renal tubular epithelium; renal tubular pigment necrosis; and nephrotubular casts and hemoglobin casts in the renal tubules.¹

Differential diagnoses

Differential diagnoses include other common toxicoses: brassicaceous vegetables, propylene glycol, acetaminophen, benzocaine, vitamin K₃, dl-methionine, naphthalene, zinc, and copper. Common feline disorders associated with Heinz body formation include diabetes mellitus, particularly if ketoacidosis is present; hepatic lipidosis; hyperthyroidism; and lymphoma and other neoplasms.

Diagnosis and treatment

Allium species toxicosis is typically diagnosed through a combination of history, clinical signs, and microscopic confirmation of a Heinz body-type hemolytic anemia.

No specific antidote is available for *Allium* species toxicosis. Treatment involves gastrointestinal decontamination and removing the *Allium* species source, treating the anemia, and providing general supportive care. Inducing emesis can be valuable in asymptomatic dogs and cats provided no complicating factors are present and ingestion was within the last one or two hours. Consider administering activated charcoal after emesis. In severely affected animals, a blood transfusion and supplemental oxygen therapy may be required. Administering intravenous crystalloids is indicated if extensive vomiting and diarrhea have occurred or if hemoglobinuria or hypotension is evident.

Carefully monitor the patient's erythron for several days after ingestion since that is when the anemic nadir usually occurs. Antioxidants, such as sodium ascorbate, vitamin E, and N-acetylcysteine, have minimal overt protective effects in onion powder toxicosis in cats.¹⁴ Diets low in potential oxidants are recommended; semimoist foods that contain propylene glycol should be avoided, particularly in cats.¹⁵ ►

RIMADYL® (carprofen)

Coated/Chewable Tablets

For oral use in dogs only

Sterile Injectable Solution 50 mg/mL

For subcutaneous use in dogs only

Non-steroidal anti-inflammatory drug

CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION: Rimadyl (carprofen) is a non-steroidal anti-inflammatory drug (NSAID) of the propionic acid class that includes ibuprofen, naproxen, and ketoprofen.

INDICATIONS: Rimadyl is indicated for the relief of pain and inflammation associated with osteoarthritis and for the control of postoperative pain associated with soft tissue and orthopedic surgeries in dogs.

CONTRAINDICATIONS: Rimadyl should not be used in dogs exhibiting previous hypersensitivity to carprofen or other NSAIDs.

PRECAUTIONS: As a class, cyclooxygenase inhibitory NSAIDs may be associated with gastrointestinal and renal toxicity. Effects may result from decreased prostaglandin production and inhibition of the enzyme cyclooxygenase which is responsible for the formation of prostaglandins from arachidonic acid. When NSAIDs inhibit prostaglandins that cause inflammation they may also inhibit those prostaglandins which maintain normal homeostatic function. These anti-prostaglandin effects may result in clinically significant disease in patients with underlying or pre-existing disease more often than in healthy patients. NSAID therapy could unmask or worsen disease which has previously been undiagnosed due to the absence of apparent clinical signs. Patients with underlying renal disease for example, may experience exacerbation or decomposition of their renal disease while on NSAID therapy. The use of parenteral fluids during surgery should be considered to reduce the potential risk of renal complications when using NSAIDs perioperatively.

Carprofen is an NSAID, and as with others in this class, adverse reactions may occur with its use. The most frequently reported effects have been gastrointestinal signs. Events involving suspected renal, hematologic, neurologic, dermatologic, and hepatic effects have also been reported. Patients at greatest risk for renal toxicity are those that are dehydrated, are concurrent diuretic therapy, or those with renal, cardiovascular, and/or hepatic dysfunction. Concurrent administration of potentially nephrotoxic drugs should be approached cautiously with appropriate monitoring. Since many NSAIDs possess the potential to induce gastrointestinal ulceration, concurrent use of Rimadyl with other anti-inflammatory drugs, such as corticosteroids and NSAIDs, should be avoided or very closely monitored. Sensitivity to drug-associated adverse reactions varies with the individual patient. For example, Rimadyl treatment was not associated with renal toxicity or gastrointestinal ulceration in well-controlled safety studies of up to ten times the dose in dogs.

Rimadyl is not recommended for use in dogs with bleeding disorders (e.g., Von Willebrand's disease), or safety has not been established in dogs with these disorders. The safe use of Rimadyl in animals less than six weeks of age, in pregnant dogs, dogs used for breeding purposes, or in lactating bitches has not been established. Safety has not been established for IV or IM administration. Studies to determine the activity of Rimadyl when administered concurrently with other protein-bound or similarly metabolized drugs have not been conducted. Drug compatibility should be monitored closely in patients requiring additional therapy. Such drugs commonly used include cardiac, anticonvulsant and behavioral medications. It has been suggested that treatment with carprofen may reduce the level of analgesic needed; this is suggested to use different class for additional injections. If additional pain medication is warranted after administration of the last daily dose of Rimadyl, alternative analgesia should be considered. The use of another NSAID is not recommended.

INFORMATION FOR DOG OWNERS: Rimadyl, like other drugs of its class, is not free from adverse reactions. Owners should be advised of the potential for adverse reactions and be informed of the clinical signs associated with drug intolerance. Adverse reactions may include decreased appetite, vomiting, diarrhea, dark or tarry stools, increased water consumption, increased urination, pale gums due to anemia, yellowing of gums, skin or whites of the eye due to jaundice, lethargy, incoordination, seizures, or behavioral changes.

Severe adverse reactions associated with this drug class can occur without warning and in rare instances result in death (see Adverse Reactions). Owners should be advised to discontinue Rimadyl therapy and contact their veterinarian immediately if signs of intolerance are observed. The vast majority of patients with drug related adverse reactions have recovered when the signs are recognized, the drug is withdrawn, and veterinary care, if appropriate, is initiated. Owners should be advised of the importance of periodic follow up for all dogs during administration of any NSAID.

WARNINGS: Keep out of reach of children. Not for human use. Consult a physician in case of accidental ingestion by humans. For use in dogs only. Do not use in cats.

All dogs should undergo a thorough history and physical examination before initiation of NSAID therapy. Appropriate laboratory tests to establish hematological and serum biochemical baseline data prior to, and periodically during, administration of any NSAID should be considered. Owners should be advised to observe for signs of potential drug toxicity (see Information for Dog Owners and Adverse Reactions).

ADVERSE REACTIONS: During investigational studies with twice-daily administration of 1 mg/lb, no clinically significant adverse reactions were reported. Some clinical signs were observed during field studies (n=283) which were similar for carprofen- and placebo-treated dogs. Incidence of the following were observed in both groups: vomiting (7%), diarrhea (6%), changes in appetite (5%), lethargy (1.4%), behavioral changes (1%), and constipation (0.3%). The product vehicle served as control. There were no serious adverse events reported during clinical field studies with once-daily oral administration of 2 mg/lb. The following categories of abnormal health observations were reported. The product vehicle served as control.

Percentage of Dogs with Abnormal Health Observations Reported in Clinical Field Study (2 mg/lb once daily)

Observation	Rimadyl (n=128)	Placebo (n=132)
Inappetence	1.9	1.5
Vomiting	3.1	3.8
Diarrhea/Soft stool	3.1	4.5
Behavior change	0.8	0.8
Dermatitis	0.8	0.8
PURO	0.8	—
SAP increase	7.8	8.3
ALT increase	5.4	6.5
AST increase	2.3	0.8
BUN increase	3.1	1.5
Bilirubinemia	19.3	18.1
Ketoneuria	16.7	6.1

Clinical pathology parameters listed represent reports of increases from pre-treatment values; medical judgment is necessary to determine clinical relevance.

During interventional studies of surgical pain for the coxib formulation, no clinically significant adverse reactions were reported. The product vehicle served as control.

Percentage of Dogs with Abnormal Health Observations Reported in Surgical Pain Field Studies with Coxibs (1 mg/lb once daily)

Observation*	Rimadyl (n=148)	Placebo (n=148)
Vomiting	12.1	13.4
Diarrhea/Soft stool	8.1	9.9
Colic or Discomfort	3.7	0
Inappetence	1.4	0
Dermatitis/Skin Lesion	2.8	1.0
Dysphagia	0.7	0
Anemia	1.4	0
Oral/Pedicular disease	1.4	0
Pyrexia	0.7	1.0
Urinary tract disease	1.4	1.0
Wound drainage	1.4	0

*A single dog may have experienced more than one occurrence of an event.

During interventional studies for the chewable tablet formulation, gastrointestinal signs were observed in some dogs. These signs included vomiting and soft stools.

There were no serious adverse events reported during clinical field studies for the injectable formulation. The following categories of abnormal health observations were reported. The product vehicle served as control.

Percentage of Dogs with Abnormal Health Observations Reported in Clinical Field Studies with the Injectable

Observation*	Rimadyl (n=114)	Placebo (n=110)
Vomiting	12.1	9.2
Diarrhea/Soft stool	2.4	3.7
Dermatitis	0.8	1.2
Dysphagia	0.8	0.9
Swelling	0	1.8
Dehydration	1.2	0
WBC increase	13.7	9.7

*A single dog may have experienced more than one occurrence of an event.

Post-Approval Experience:

Although not all adverse reactions are reported, the following adverse reactions are based on voluntary post-approval adverse drug experience reports. The categories of adverse reactions are listed in decreasing order of frequency by body system.

Gastrointestinal: Vomiting, diarrhea, constipation, inappetence, melena, hematemesis, gastrointestinal ulceration, gastrointestinal bleeding, proctocolitis.

Hepatic: Inappetence, vomiting, jaundice, acute hepatic failure, hepatic enzyme elevation, abnormal liver function tests, hyperbilirubinemia, bilirubinuria, hypoproteinemias. Approximately one-third of hepatic reports were in Labrador Retrievers.

Neurologic: Anemia, paresis, paralysis, seizures, vestibular signs, disorientation.

Urinary: Hematuria, polyuria, polydipsia, urinary incontinence, urinary tract infection, azotemia, acute renal failure, tubular nephropathies (including acute tubular necrosis, renal tubular atrophy, glomerulonephritis).

Behavioral: Sedation, lethargy, hyperaesthesia, restlessness, aggressiveness.

Hematologic: Immune-mediated hemolytic anemia, immune-mediated thrombocytopenia, blood loss anemia, apertosis.

Dermatologic: Pruritus, increased shedding, alopecia, pyodermitis, moist dermatitis (hot spots), necrotizing pemphigus/vasculitis, vesical acrylamidosis.

Immunologic or hypersensitivity: Facial swelling, hives, erythema. In rare situations, death has been associated with some of the adverse reactions listed above.

For a copy of the Material Safety Data Sheet (MSDS) call 1-800-352-5900.

To report adverse reactions call Pfizer Animal Health at 1-800-368-5288.

NADA #141-050, NADA #141-111, NADA #141-388 Approved by FDA.

Injectable Manufactured by: Venkova Limited, Dundee, United Kingdom



continued

A patient's prognosis depends on the species of plant involved, the severity of the anemia, and the institution of supportive care. In companion animals, avoiding exposure is the best preventive strategy. Feeding pets onions or other *Allium* species or their derivatives should be stopped.

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