

PEER-REVIEWED

Helping animals exposed to the herbicide paraquat

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Last summer, an epizootic of paraquat poisoning caused the deaths of at least seven dogs in Portland, Ore.¹ This epizootic is evidence that this type of poisoning remains a current problem in companion-animal practice in North America. Paraquat, a poisonous dipyrindilium compound, is one of the few nonselective herbicides still available in the United States. Because paraquat is fast-acting, can be effectively used in wet environments, and has limited potential for environmental contamination and low rates of weed resistance, it is still widely used in various crop production systems. However, paraquat is highly toxic to domestic animals if ingested.^{2,3}

Sources

Within the United States, paraquat is a restricted-use herbicide with the exception of pressurized spray formulations that contain no more than 0.44% paraquat bis (methyl sulfate) and liquid fertilizer formulations that contain no more than 0.04% paraquat dichloride. Current active U.S. registered brand names include Gramoxone Super (Syngenta), Gramoxone Max (Syngenta), Cyclone Max (Syngenta Crop Protection), Marman Herbiquat Herbicide (Marman

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This article from *The Oregonian* on Aug. 18, 2004, describes the discovery of meat and raw chicken that may have been planted to harm dogs in a Portland, Ore., public park. As of Sept. 2, officials ruled out paraquat poisoning in this case, and test results for other toxins are pending. Portland residents are wary because of last year's incidents of paraquat poisoning in an off-leash dog park that resulted in the deaths of at least seven animals.

USA), and Surefire Herbicide (UAP-Loveland Products). Because paraquat has been available for agricultural use since 1962, outdated stocks are relatively easy to obtain.² Older, outdated domestic garden herbicides often contained a 50:50 (Wt:Wt) mixture of diquat and paraquat, and supplies of this mixture can still be found in the United States. Despite paraquat's restricted-use status, intentional paraquat poisoning of animals remains a problem.^{3,4}

Exposure and toxicokinetics

Most cases of paraquat poisoning in people and animals involve ingestion of concentrated formulations.^{2,8} In dogs, only about 25% to 28% of orally administered paraquat is absorbed; the remainder is excreted unchanged in the feces.² In experiments in rodents, paraquat was

detected in the feces up to seven days after exposure.² The oral LD₅₀ of paraquat in cats is 35 to 50 mg/kg. The oral LD₅₀ in dogs is unknown but is higher than that in cats, and the intravenous LD₅₀ in dogs is 7.48 mg/kg.

Many of the current commercial paraquat preparations (e.g. Gramoxone) deliberately incorporate emetics and bitter-tasters in their concentrate formulations to reduce the dose absorbed after suicide-related oral poisoning in people.^{2,9} This protective measure causes fasting and nonfasting dogs to vomit 61% to 86% of an orally administered dose and reduces blood paraquat concentrations by about 170 times.⁹ Unfortunately, older concentrates are less likely to incorporate this key safety feature.

Irrespective of the administration route, absorbed and circulating paraquat is rapidly, selectively, and actively

sequestered in type I and type II alveolar cells and Clara cells by an energy-dependent diamine/polyamine transport mechanism that follows saturation kinetics.¹⁰ The lungs have the greatest paraquat retention and, thus, the highest concentration of paraquat of any of

cycling produces oxygen and hydroxyl, and the ensuing free-radical-mediated damage to cellular macromolecules, particularly membrane lipids, is primarily responsible for paraquat's toxic effects.² Tissue damage is typically confined to selective paraquat accumulation

triointestinal upset, particularly vomiting, since paraquat is a gastrointestinal irritant.^{3-6,8} Other common clinical signs include anorexia, inappetence, and lethargy. These clinical signs, frequently combined with a history of consumption of unknown food items, often lead to an initial misdiagnosis of acute gastroenteritis. The inclusion of emetics in concentrated paraquat formulations may increase the risk of misdiagnosis.

Clinical experience gained during the recent outbreak in Portland demonstrates that elevated serum lipase activities are common at presentation. This elevation may lead to an initial presumptive diagnosis of acute pancreatitis. Stasis of the pancreatic duct, pancreatic failure, and elevated serum amylase activities have been detected in cases of paraquat poisoning in people.¹⁴⁻¹⁶ In people, the severity of pancreatic injury at the time of initial treatment helps to predict survival from acute paraquat poisoning.¹⁵ However, serum lipase activities are also commonly increased in dogs with compromised renal function.¹⁷ Thus, hyperlipasemia may be a secondary consequence of paraquat-induced acute renal failure rather than the result of direct damage to the exocrine pancreas.

Concentrated paraquat solutions cause severe irritation to the skin and mucous membranes; oropharyngeal pain and swelling followed by ulceration and mucosal sloughing a few days later are common.² In extreme cases, complete sloughing and perforation of the esophagus can occur.

Evidence of compromised renal function (*i.e.* increased blood urea nitrogen and creatinine concentrations) and mild systemic hypertension are also often present at admission. Death after paraquat ingestion is typically caused by an insidious and irreversible form of respiratory failure. The time of

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the tissues four hours after ingestion.² At four hours, the paraquat concentration in the lungs is about 10 times higher than at other selective accretion sites (*e.g.* kidneys, brain, adrenal glands).² By four to 10 days after exposure, the paraquat concentration in the lungs is about 30 to 80 times higher than in plasma. The half-life of paraquat in the lungs is about 24 hours. Because of paraquat's rapid excretion, the paraquat concentration in the lungs and other tissues may fall below detectable limits in animals that die of this agent's delayed effects.^{2,3,11}

Systemically circulating paraquat is actively excreted by renal proximal tubules by using a divalent/polyvalent organic cation/hydrogen ion exchanger mechanism.^{2,12,13} In rodents, urine paraquat concentrations rapidly decrease over the first 24 hours after ingestion. But paraquat can be detected in rodent urine up to 15 days after ingestion, despite the absence of detectable paraquat concentrations in the serum.²

Mechanism of action

Although paraquat is excreted largely unchanged, it undergoes extensive cyclic oxidation-reduction reactions in mammalian tissues *in vivo*. This redox

sites (*e.g.* type I and type II alveolar cells, Clara cells, renal proximal tubular epithelia). Contact of mucosal surfaces and skin with concentrated paraquat solutions may also result in marked tissue damage.

Clinical signs and diagnostic tests

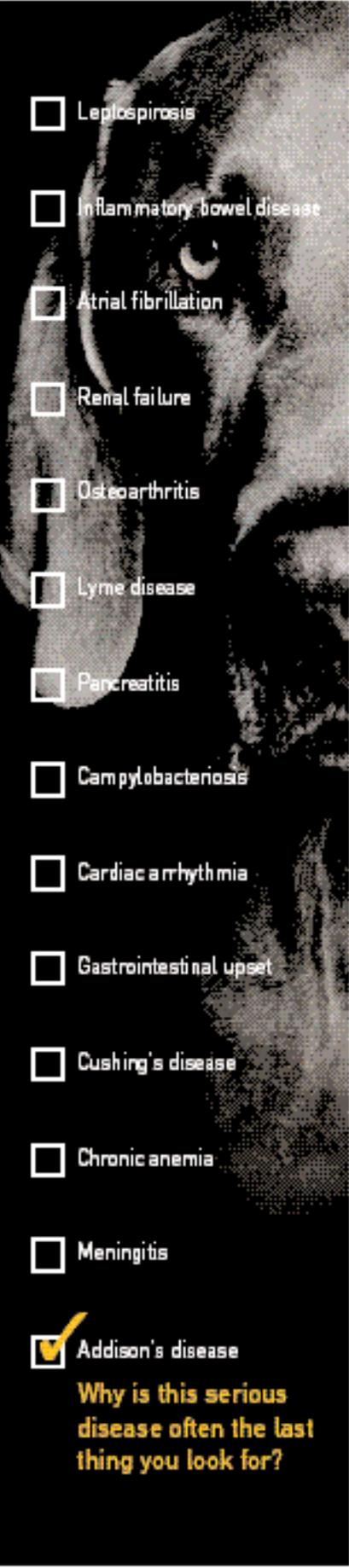
Single-dose paraquat poisoning has been classified into three dose-related syndromes²:

1. High-dose, fulminant, systemic poisoning with death occurring one to four days after ingestion due to a combination of acute pulmonary edema, renal failure, hepatocellular damage, necrosis of both intrahepatic and extrahepatic bile ducts and the gallbladder, adrenal failure, and biochemical disturbances;
2. Subacute poisoning with a slower onset of organ failure and eventual death from pulmonary edema and respiratory failure;
3. A low-dose, late, irreversible pulmonary fibrosis syndrome with death ensuing several days to several weeks after exposure.

Typically, early clinical signs of paraquat toxicosis involve acute gas-

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continued

- 
- Leptospirosis
 - Inflammatory bowel disease
 - Atrial fibrillation
 - Renal failure
 - Osteoarthritis
 - Lyme disease
 - Pancreatitis
 - Campylobacteriosis
 - Cardiac arrhythmia
 - Gastrointestinal upset
 - Cushing's disease
 - Chronic anemia
 - Meningitis
 - Addison's disease

Why is this serious disease often the last thing you look for?

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onset of the respiratory syndrome after paraquat poisoning is dose-related and may occur a few days to more than a week after exposure.²

It is uncommon to detect abnormalities by thoracic radiographic examination at the early stages of the paraquat-induced respiratory syndrome; however, thoracic radiographs may provide useful information during the later stages. In people, thoracic abnormalities that are detectable by radiography the first week after paraquat ingestion include a bilateral ground-glass pulmonary shadow, diffuse consolidation, pneumomediastinum with or without pneumothorax, and cardiomegaly with widening of the superior mediastinum.¹⁸⁻²⁰

Histopathologic lesions

Histologic evidence of widespread pulmonary alveolar damage, hemorrhage, and edema are typical of the early stages of paraquat poisoning in dogs.^{2,3} The classic progression of lung changes in people starts with detachment or necrosis of alveolar type I and type II cells, edema, and hemorrhage. These changes are followed by the proliferation of fibroblasts and polymorphic cells, the loss of surfactant secretion, attempts at re-epithelialization of the alveolar surface, and eventual thickening of the alveolar septa from interstitial fibrosis. In people that survive the acute phases of paraquat toxicosis, marked pulmonary fibrosis usually develops two or three weeks after ingestion.²

Selective accumulation in the kidneys is associated with dose-related damage to the renal proximal tubules.^{2,3,11,21} Evidence of tubular regeneration is often present if a patient survives the initial stages of paraquat toxicosis.^{2,3,11,21}

Diagnosis

Paraquat toxicosis is usually diagnosed through a combination of clinical history, the results of a histologic examination of affected tissues, and detection of paraquat in tissue or bait samples. Spectrophotometry, gas and liquid chromatography, and radioimmunoassay have all been used to measure paraquat concentrations in biologic fluids; however, because prompt recognition of paraquat poisoning is a key factor in its treatment, using fast qualitative tests based on the dithionite reaction (*i.e.* dithionite spot test) may offer an important advantage.³ In the acute stages of paraquat poisoning, vomitus, gastric contents, bait or concentrate samples, feces, and lung and renal tissue are ideal samples. Blood or plasma may be tested, but circulating paraquat concentrations are much lower in blood and plasma than concentrations in the lungs.

Treatment

Currently, no specific antidote for paraquat poisoning is available. The most important determinant of survival after ingestion is early treatment.² Treatment must be instituted within hours of exposure to be effective. The initial treatment priorities for paraquat poisoning are administering an adsorbent to neutralize ingested paraquat and removing the poison by emesis or gastric lavage. Traditionally, fuller's earth (*i.e.* attapulgite clay, calcium montmorillonite) or bentonite (*i.e.* sodium montmorillonite) adsorbents have been used. Keep in mind that the adsorbent capacity of fuller's earth varies among manufacturers and that only highly adsorbent, pharmaceutical-grade preparations should be used.²²

Experimental studies have demon-



Caution: Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.

Indications: For use as replacement therapy for the mineralocorticoid deficit in dogs with primary adrenocortical insufficiency.

Effectiveness: Results of two 75-day clinical studies in dogs with primary hypoadrenocorticism, each treated with three doses of PERCORTEN-V, demonstrated return to normal sodium/potassium ratios in 96% of dogs in one study and 100% of dogs in the other study. See the full product insert for more information.

Description: The active ingredient in PERCORTEN-V is desoxytocorticosterone pivalate (DOCP). It is a mineralocorticoid hormone and an analog of desoxytocorticosterone. Its effects are dependent on a functioning kidney. Animals suffering from hyporexia, polydipsia, pre-renal azotemia, and inadequate tissue perfusion must be rehydrated with intravenous fluid (saline) therapy before starting PERCORTEN-V therapy. Primary renal disease should be ruled out before starting PERCORTEN-V therapy.

Warnings: Do not use this drug in pregnant dogs. Do not use in dogs suffering from congestive heart disease, severe renal disease or colitis.

Keep this and all drugs out of the reach of children. In case of human consumption, contact a physician or Poisons Control Center immediately.

Precautions: Some patients are more sensitive to the actions of PERCORTEN-V and may exhibit side effects in an exaggerated degree. Some patients may show signs of hypotension or hypokalemia. The dosage of PERCORTEN-V should be reduced in these patients.

Like other adrenocortical hormones, PERCORTEN-V may cause severe side effects if dosage is too high or prolonged. It may cause polyuria, polydipsia, increased blood volume, edema and cardiac enlargement.

Excessive weight gain may indicate fluid retention secondary to sodium retention. PERCORTEN-V should be used with caution in patients with congestive heart disease, edema or renal disease.

Adverse Reactions: The following adverse reactions have been reported following the use of PERCORTEN-V: depression, polyuria, polydipsia, anorexia, skin and coat changes, diarrhea, vomiting, weakness, weight loss, incoordination, pain on injection and injection site abscess. Some of these effects may resolve with adjustments in dose or interval of PERCORTEN-V or concomitant glucocorticoid medication.

Safety: PERCORTEN-V was administered to healthy Beagles at 0, 2.2, 6.6 or 11 mg/kg of body weight daily over a consecutive 3-day period every 28 days (equivalent to a cumulative monthly dosage of 0, 6.6, 19.8 or 33 mg/kg) for 6 months. This resulted in no mortality or any significant effects on body weight, food consumption, and ophthalmic observations at any dose level. However, polyuria and polydipsia were noted and creatinine concentration decreased (14-89 mg/dl) in the 1X, 2X and 5X groups. Generalized nephropathy was only observed in the kidneys when PERCORTEN-V was administered at 6.6 mg/kg or higher. PERCORTEN-V was well tolerated when administered at 2.2 mg/kg on three consecutive days in every 28-day period for six months.

Dosage and Administration: PERCORTEN-V suspension is to be injected intramuscularly. Care should be used to prevent inadvertent intravenous injection, which may cause acute collapse and shock. PERCORTEN-V only replaces mineralocorticoid hormones. Glucocorticoid replacement must be supplied by small daily doses of glucocorticoid hormones (e.g., prednisone or prednisolone) (0.2-0.4 mg/kg/day).

Failure to administer glucocorticoids is the most common reason for treatment failure. Animals receiving PERCORTEN-V do not require oral salt supplementation. Dosage requirements must be individualized based on patient's response to therapy. Begin treatment with PERCORTEN-V at a dose of 1.0 mg per pound of body weight every 25 days. In some patients the dose may be reduced. Serum sodium and potassium levels should be monitored to assure the animal is properly compensated. Most patients are well controlled with a dose range of 0.75 to 1.0 mg per pound of body weight, given every 21 to 30 days. See the full product insert for more information.

How Supplied: Multiple-Dose vials, packed one vial per carton.

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strated that activated charcoal is an effective in vivo paraquat adsorbent. Activated charcoal's in vitro binding of paraquat is equivalent to that of fuller's earth.²³ Thirty percent activated charcoal administered as an aqueous oral slurry is as effective as 30% fuller's earth administered as an aqueous oral slurry in reducing the systemic absorption of paraquat up to one hour after ingestion.²⁴ In cases of experimental paraquat poisoning in rodents, concomitantly administering activated charcoal and magnesium citrate improved the survival rate.²³ Since fuller's earth and bentonite are usually not on hand, it's better to go ahead and administer activated charcoal.²⁵ In an emergency, pulverized clay-based cat litter has also been suggested as an alternative adsorbent.²⁵ Cation exchange resins, such as sodium polystyrene sulfonate (Kayexalate—Sanofi-Synthelabo), have much higher paraquat-binding capacities than other adsorbents, increase the LD₅₀ up to 2.1 times in rats, and improve survival rates in people.²⁶ Unfortunately, these materials are not routinely available in veterinary practice. Because of the risk of esophageal perforation, use extreme care when administering adsorbents through a stomach tube.

Because systemically absorbed paraquat is eliminated primarily through renal excretion and the presence of oliguric renal failure markedly contributes to paraquat accumulation in the lungs, maintaining urine production is critical when treating an animal with paraquat toxicosis.² Forced diuresis can remove large quantities of circulating paraquat if it is initiated within a day or so of ingestion.^{2,27-30} However, forced diuresis carries with it the risks of electrolyte disturbances and exacerbation of paraquat-induced pulmonary edema. Particular caution is required

during the first 24 hours after ingestion, especially if oliguria is present.²

Antioxidant therapy has been extensively studied in experimental models and cases involving people with paraquat toxicosis with variable results.³¹ Recent studies using trimetazidine (an anti-ischemic), S-carboxymethylcysteine (a respiratory drug), propofol, and epigallocatechin gallate (from green tea) have shown promising results, but clinical experience with these agents is limited, and little controlled clinical trial data are available.³¹⁻³⁴ Because of the risk of enhanced oxidative effects, oxygen administration in patients with paraquat toxicosis should be avoided except when necessary for comfort (e.g. patients in respiratory distress).² Hypoxic ventilation has been used in paraquat poisoning cases in people, but its effectiveness has not been extensively studied.^{35,36} Collagen synthesis inhibitors may offer some control or prevention of pulmonary fibrosis, but their use has not been extensively studied in field conditions.³⁷ Corticosteroids, immunosuppressants, vitamins, β -blockers, alkylating agents, chlorpromazine hydrochloride, α -tocopherol, superoxide dismutase, glutathione peroxidase, and nitric oxide inhalation have all been used to treat paraquat toxicosis with little clearly documented effectiveness.^{2,14,38,39} Currently available immuno-antidotes are ineffective.⁴⁰

Prognosis and prevention

Despite treatment, the overall prognosis for paraquat toxicosis is poor. Disappointingly, survival from paraquat poisoning may be more strongly associated with the circumstances of the poisoning rather than any treatment administered.³⁵ Situational factors as-

sociated with higher survival rates in people include inhalation or dermal exposure, ingestion of less than 35 mg/kg, a young age at the time of poisoning, the time between paraquat ingestion and the last meal (because paraquat is adsorbed and neutralized by foodstuffs), accidental ingestion rather than homicidal intention, ingestion of diluted materials rather than liquid concentrates or granular formulations, and aggressive treatment within two to five hours of ingestion.^{2,15,28,35} In people, a lack of caustic gastric lesions; lower urine and plasma paraquat concentrations; lesser degrees of leukocytosis, acidosis, and respiratory distress; and absence of renal, hepatic, and pancreatic failure at the time of admission are all considered to be good predictors of survival.^{15,28,35}

Because of the severe consequences of paraquat toxicosis, early diagnosis and aggressive treatment are paramount if the survival prospects of a severely poisoned patient are to be improved. Given the limited effectiveness of current treatment modalities, the best solution to the problem of paraquat poisoning in companion animals is to prevent exposure.

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