

GRAPE AND RAISIN TOXICITY IN DOGS

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Beginning in 1989, veterinarians at the American Society for the Prevention of Cruelty to Animals Animal Poison Control Center (APCC; www.aspc.org/apcc) began to notice a new trend in calls. There appeared to be a relationship between grape or raisin ingestion in dogs and the onset of vomiting and acute kidney failure. Since then, a definitive cause-and-effect relationship has been identified. However, questions remain concerning raisin and grape toxicity, including the exact toxic principle as well as the mechanism of action responsible for the toxicity.

The toxic component does appear to be water soluble and located within the flesh of the grape. Both seeded and seedless, store bought and home grown, as well as grapes of any brand or region in the United States, have been associated with toxicity. Grape seed extract appears to be innocuous, but the safety of grape juice has yet to be determined, and at this point, it is recommended that administration to pets be avoided. Several cases have been documented in dogs, and there are anecdotal reports of toxicity in cats. In the documented cases, the dose ingested was not related to the severity of clinical signs or outcome. A border collie survived after eating a 16-oz box of raisins and receiving peritoneal dialysis, but a Labrador retriever died after ingesting a 20-oz box of raisins and also undergoing peritoneal dialysis. There does not seem to be a connection between the type of product ingested and outcome, either, because death has occurred from ingestion of various amounts of both grapes and raisins. At this time, the minimum dose reported to cause toxicity in dogs is 0.7 oz/kg of grapes and 0.11 oz/kg of raisins.

Clinical signs seen with raisin and grape toxicity usually involve the gastrointestinal system and kidneys. Vomiting typically starts within several hours of ingestion. Within 18 to 36 hours, acute renal failure may occur because of damage to the tubular epithelial cells. Unless the toxic potential of these products is realized, these initial signs may be treated symptomatically as an acute gastritis that does not resolve. It is vital to realize that the ingestion of grapes or raisins, even a small amount, can cause lethal damage to the kidneys. The sooner this is realized and addressed in these patients, the better.

A recent study looked at 43 dogs that were presented for signs associated with grape or raisin toxicity. The mortality rate of this group was 47%. Of these, euthanasia was elected in 35% of cases, and 12% of the dogs died despite treatment. In dogs that did recover, most regained kidney function by 180 days after ingestion. A separate report by the APCC found that between April 2003 and April 2004, 140 cases of ingestion were reported. Of these, more than 50 dogs developed clinical signs, but only seven died. The reason for this difference in survival rates is unknown.

DIAGNOSTIC CRITERIA

Historical Information

- Owners are often unaware of the danger involved in feeding their pets grapes or raisins. Not knowing any better, they frequently feed these foods as treats.
- Dogs may get into the garbage or cupboards to ingest these products or may eat grapes directly from grapevines.

Gender/Age/Breed Predisposition

None.

Owner Observations

- Vomiting, typically within several hours of ingestion.
- Diarrhea.
- Partially digested grapes or raisins may be present in the vomitus or fecal matter.
- Lethargy.
- Anorexia.
- Ataxia; trembling.
- Polyuria and polydipsia during the initial period; may turn into oliguria or anuria if the damage is severe enough.

Other Historical Considerations/Predispositions

- Some animals seem to be more at risk for developing the renal toxic effects of grapes and raisins; for unknown reasons, certain animals are able to toler-

ate ingestion of larger amounts with no apparent problems. Whether this is caused by a difference in the actual product ingested or in the way the product is handled within the individual animal has yet to be determined.

- Concurrent illness or administration of other potentially nephrotoxic drugs (aminoglycosides, NSAIDs) may predispose animals to disease manifestation.

Physical Examination Findings

- Clinical signs can range from a normal, bright, alert, and responsive mentation to obtunded or comatose depending on the time since ingestion and dose ingested.
- Vital signs usually within normal limits.
- Dehydration.
- Abdominal pain.
- Ptyalism.
- Ataxia; trembling.
- Peripheral edema if overhydration from oliguria or anuria is present.

Laboratory Findings

Chemistry Panel \$

- **Increased:**
 - Creatinine (reference range, 0–1.3 mg/dl).
 - Blood urea nitrogen (BUN; reference range, 10–25 mg/dl).
 - Phosphorus (reference range, 3.3–5.8 mg/dl).
 - Calcium, total and ionized (reference ranges, 9.5–11.8 mg/dl and 1.1–1.4 mg/dl, respectively).
 - Alanine aminotransferase (reference range, 26–200 U/L).
 - Alkaline phosphatase (reference range, 4–95 U/L).
 - Amylase (reference range, 290–1125 U/L).
- **Increased or decreased:**
 - Potassium (reference range, 3.5–5.9 mEq/L).

Urinalysis \$

- Isosthenuria (defined as a specific gravity of 1.008–1.012).
- Proteinuria.
- Microscopic hematuria.
- Mixed crystalluria.
- Granular or hyaline casts.

Complete Blood Count \$

- As disease progresses, anemia or thrombocytopenia may be evident.
 - Normal packed cell volume, 35% to 45%; normal platelets, 165,000–500,000/ μ l.

Coagulation Profile \$

- Coagulation times have been prolonged in some reported cases:
 - Activated clot time (reference range, 120–180 sec).
 - Prothrombin time (reference range dependent on machine).
 - Activated partial thromboplastin time (reference range dependent on machine).
- Increased fibrinogen (reference range, 100–300 mg/dl).
- Increased fibrin/fibrinogen degradation products (reference range, <5 μ g/dl) or D-dimers (reference range <250 ng/ml).
- Thrombocytopenia.

Other Diagnostic Findings

Abdominal Ultrasonography \$-\$\$

- Enlarged kidneys.
- Hyperechoic renal cortices.
- Decreased corticomedullary differentiation.
- Medullary rim sign, or a slight increased echogenicity at the corticomedullary junction. This sign can be seen with certain disease states or can be found in normal kidneys.

Hypertension \$

- Increased systolic (reference range, 100–150 mm Hg), diastolic (reference range, 60–80 mm Hg), or mean arterial (reference range, 80–120 mm Hg) blood pressures.

Renal Biopsy \$-\$\$\$

- Ultrasound-guided or surgically obtained via laparotomy or keyhole approach.
- Diffuse, nonspecific proximal renal tubular degeneration.
- Proteinaceous debris or golden-brown pigment in tubules.
- Interstitial nephritis (neutrophils and lymphocytes).

Summary of Diagnostic Criteria

- Known or suspected exposure to raisins or grapes within the previous 48 hours.
- Severe azotemia.
- Hyperphosphatemia.
- Isosthenuria.
- Proximal renal tubular degeneration on biopsy.

Diagnostic Differentials

Leptospirosis

- Positive titers or polymerase chain reaction test results on serum or urine.

ON THE NEWS FRONT

Enteral dialysis is becoming a more popular treatment for any patient with kidney disease resulting in elevated BUN and creatinine. The main product, Azodyl (formerly Kibow) is available through Vétoquinol USA (Buena, NJ). This is a probiotic product—basically, a formulation of safe, live bacteria—that acts to decrease the amount of protein breakdown product that is able to be absorbed in the bloodstream, decreasing the load on the kidney. Its true effectiveness has yet to be proven. Dosage should be via label directions.

- In the early acute disease state, titers can be negative if blood is drawn before antibodies have had time to form. If initial titers are negative, testing should be repeated in 2 weeks to ensure a negative result.

Ethylene Glycol Toxicity

- Positive ethylene glycol plasma test result.
- Low calcium level.
- Increased osmolar gap.
- Increased anion gap.
- Calcium oxalate crystalluria.
- Positive fluorescence of urine with Wood's lamp.

NSAID Toxicity

- Known exposure or high index of suspicion.
- Predominant gastrointestinal effects consisting of bloody vomit or diarrhea in addition to signs of kidney disease.

Addisonian Crisis

- Na:K ratio of <27 is suspicious; <23 is suggestive.
- Decreased to absent response to adrenocorticotropic hormone stimulation test.
- Azotemia is typically not severe and responds well to fluid diuresis.
- No oliguria or anuria if the patient is properly hydrated.
- High calcium level.
- Low albumin level.

TREATMENT RECOMMENDATIONS

Initial Treatment

- **If ingestion is caught early**, gastric decontamination procedures should be attempted.

—Induction of emesis if less than 2 to 4 hours have passed since ingestion.

- **Apomorphine:** Either 0.03 mg/kg IV, 0.04 mg/kg IM, or 0.08 mg/kg IM. As an alternative, one tablet can be placed in the conjunctival sac and then rinsed out with saline after emesis is induced. \$
- **Hydrogen peroxide:** Can be used as an alternative to apomorphine, although efficacy may be decreased. Dose is 1–2 ml/kg PO with a second dose at 10 minutes if no vomiting. \$

—**Activated charcoal:** Recommended to give with a cathartic, either in the same product or separately. Dose is 1–4 g/kg q4–6h over a 24-hour period. \$

- **If clinically normal but known exposure:** IV fluid administration using a balanced electrolyte solution or 0.9% NaCl should be instituted. Diuresis at a rate of 90 to 120 ml/kg/day (1.5 to 2.0 times the maintenance rate) should be continued for at least 48 hours. If BUN and creatinine are within the normal range 3 days after ingestion, it is likely that the animal will not develop any adverse consequences, and the animal can slowly be weaned off fluids. If BUN or creatinine levels are increased, diuresis should continue.
- **If clinical signs are present:** The patient should be rehydrated over a 4- to 6-hour period (assuming cardiovascularly normal) and then continued at a rate of 90 to 180 ml/kg/day (1.5 to 3 times the maintenance rate) for at least 48 to 72 hours. Blood work can be checked at this time, and if the BUN and creatinine remain within the normal range, it is unlikely that any serious damage has been done, and fluids can be gradually weaned off. However, if there are alterations in the kidney enzymes, fluid therapy should be continued and treatment for acute kidney failure instituted (see below).
- Placement of a **central venous catheter** for monitoring of central venous pressure (CVP) is very helpful in monitoring fluid therapy and hydration status. CVP is used as an estimation of cardiac preload, which is principally made up of the intravascular volume. A low CVP implies low preload and a need for more volume or IV fluids; a high CVP implies an increase in preload and a need to decrease fluid administration and possibly initiate diuretic therapy. The CVP of a normal patient is 0 to 5 cm H₂O; however, the target during diuresis is typically between 3 and 8 cm H₂O depending on the cardiac stability of the patient.
- An **indwelling urinary catheter** attached to a closed collection system is highly recommended to accurately monitor the volume of urine output. The status of urine output is an important prognostic indicator as well as a therapeutic monitor. As urine

output decreases to oliguria or anuria (<0.5 ml/kg/hr), volume overload becomes a greater concern, and more advanced therapies such as peritoneal dialysis and hemodialysis become more of a potential next step.

Alternative/Optional Treatments/Therapy

Stimulation of Urine Output †

Various pharmacologic methods have been used in attempts to stimulate urine output, although there is little evidence of their efficacy in altering morbidity or mortality. An increase in urine output does not necessarily imply an improvement in glomerular filtration rate (GFR). Urine output should be assessed in conjunction with the patient's clinical and laboratory status to accurately assess the animal's state. A decline in urine output can also lead to life-threatening electrolyte abnormalities and fluid overload; diuretic agents are valuable in treating these conditions.

- **Mannitol** can increase blood flow to the renal tubules and decrease swelling of the renal tubular cells, which can help open up the tubular lumens, relieving obstruction. Mannitol causes an osmotic diuresis that increases the excretion of solutes and flushes out the debris in the tubular lumen. However, mannitol can dehydrate patients because of its diuretic effect, so the patient's hydration status should be monitored closely. CVP is useful for this purpose. Mannitol should not be used in animals that are at risk for or already have volume overload. In oliguric or anuric patients, mannitol can cause volume overload; thus, it should be used with caution in such patients and in conjunction with careful monitoring of urine volume, CVP, and heart rate. Urine production should increase within 20 to 30 minutes of administration if mannitol is to have an effect. Administration should be discontinued if urine production shows no change, CVP is at or increased to 8 cm H₂O or higher, or heart rate increases.

— **Dosage:** 0.5–1 g/kg IV over 20 minutes up to three times a day.

- **Furosemide**, a loop diuretic, inhibits the sodium–potassium–chloride channels in the ascending limb of the loop of Henle, helping to increase urine output in a failing but functional kidney. Although this increased production has no proven effect on morbidity or mortality associated with acute kidney failure, furosemide can be useful in managing the electrolyte and fluid status abnormalities commonly seen with acute kidney disease. It seems to be most effective when given concurrently with dopamine, but the two drugs cannot be mixed together because they will precipitate.

— **Dosage:** 2–6 mg/kg IV, IM, or SC as an initial trial dose. If urine output does not increase, additional dosages are not recommended. If urine output increases, furosemide can be continued at the above rate q4–8h as determined by clinical condition or given as a constant-rate infusion (CRI) at 0.25–1 mg/kg/min. Animals receiving high or repeated doses of furosemide tend to become hypokalemic and may require supplementation.

- **Dopamine** is a catecholamine that has dose-dependent effects. Dopaminergic receptors appear to be activated at a low dose (0.1–5 µg/kg/min); β- and α-receptor effects occur as the dose increases. Recent studies have shown a lack of improvement with dopamine use in humans with acute kidney disease. The pharmacokinetic effects of dopamine can be altered in ill patients, and the dose-dependent effects may not hold true. A low, dopaminergic dose may actually cause a vasoconstriction in some patients with significant illness, which may result in suboptimal effects on tissue, including impaired oxygenation of the kidneys.

— **Dosage:** 1–3 µg/kg/min IV as a CRI. Start at the low end of the dose range and titrate up as needed every 30 minutes.

Hemodialysis ††††

Hemodialysis should be considered in any patient that fails to show improvement or worsens after 12 to 24 hours of aggressive treatment; has life-threatening hyperkalemia or another electrolyte disorder; or has fluid overload, especially with oliguria or anuria unresponsive to medical intervention. Hemodialysis can be a lifesaving procedure, supporting the function of the kidneys while allowing them time to heal. The actual toxic property in grapes is not known at this time, but it is known that it is water soluble. If it is found to be of small molecular size, hemodialysis in the early stages of intoxication may be effective at removing the toxin before it has a chance to injure the kidneys. However, until more research is done, the efficacy of early hemodialysis in the removal of toxin remains in question. Hemodialysis is only available at a select group of specialty referral centers. Early referral to these institutions, if an option, is highly recommended for the best results despite the complications inherent in hemodialysis.

Peritoneal Dialysis ††††

Initiation of peritoneal dialysis follows the same guidelines as hemodialysis. Although peritoneal dialysis is a more widely available option, it is considered less effective and carries a significant risk to the animal.

Supportive Treatment

Drugs to Treat Vomiting and Gastric Upset

- **Metoclopramide:** Typically the first line of treatment for vomiting. Used for its prokinetic and antiemetic effects. \$
 - Intermittent injections of 0.2–0.4 mg/kg IV, IM, or SC q8h or a CRI at 1–2 mg/kg/day. CRI is recommended for more severe vomiting.
- **Chlorpromazine:** Can be used in conjunction with metoclopramide as an antiemetic. Because this drug can cause significant vasodilation and hypotension, it should not be used in dehydrated animals. \$
 - 0.5 mg/kg SC or IV q6–8h. The SC route appears to lessen the sedative and hypotensive effects associated with this drug.
- **5-HT₃ receptor blockers:** Acting on the chemoreceptor trigger zone in the central nervous system, these agents are primarily used for chemotherapy nausea but can be helpful in controlling vomiting unresponsive to other agents. \$
 - **Dolasetron:** 0.6 mg/kg IV once daily.
 - **Ondansetron:** 0.1–0.2 mg/kg IV q6–12h.
- **Antacids:** Gastritis and gastric ulcers are common with kidney disease, either from the direct effect of the uremic toxins or the hypergastrinemia that is frequently seen with decreased GFR. The toxic component of grapes and raisins may also have its own effect in causing gastritis or ulcers. \$
 - **Ranitidine:** Also has a slight prokinetic effect. The dose is 1–2 mg/kg IV, IM, or SC q12h.
 - **Famotidine:** 0.5–1 mg/kg IV, IM, or SC q12–24h.
 - **Omeprazole:** 0.5–1 mg/kg PO q12–24h. This drug is only available in the oral formulation at this time, so it is not recommended in animals with severe vomiting.
 - **Pantoprazole:** 1 mg/kg IV q24h. This is a newer injectable proton pump inhibitor. Although it appears to be quite effective, its current cost tends to be prohibitive to its use in most veterinary patients. (One dose costs approximately \$100 to \$150; this is a daily medication, making it cost prohibitive for most clients.)
- **Sucralfate:** This mucosal coating agent is helpful for binding and protecting areas of ulceration in the stomach or esophagus. The drug may bind to and affect the activity of other drugs, so it should be administered a minimum of 1 to 2 hours either before or after other oral medications. \$
 - Typically given 0.5–1.0 g q8h dissolved in water to make a slurry.

Phosphate Binders \$

Because the goal of these drugs is to decrease the phosphate absorbed from the gut, it is best to administer them with food.

- **Aluminum hydroxide:** 30–100 mg/kg/day PO.
- **Sucralfate:** Also has a slight phosphate-binding action. Typically given 0.5–1.0 g q8h dissolved in water to make a slurry.
- **Epakitin:** A newer phosphate binder classified as a nutritional supplement. It should be used only in patients with normal calcium. Dose is 1 g/5 kg over food q12h. One level dosing spoon provided is equivalent to 1.5 ml or 1.0 g of medication.

Antihypertensives \$

Hypertension is a common abnormality associated with kidney disease. If not controlled, hypertension can lead to other problems such as worsening glomerular disease, retinal detachment, or neurologic dysfunction.

- **Amlodipine:** 0.5 mg/kg PO q12–24h.
- **Angiotensin-converting enzyme inhibitors:** Although not effective in controlling severe hypertension by itself, this class of drugs is frequently the first chosen for hypertension associated with kidney disease. These drugs seem effective in helping to reduce glomerular protein loss as well as delaying the progression of renal insufficiency. Acute exacerbation of kidney failure may be seen in some cases.
 - **Enalapril:** 0.25–0.5 mg/kg PO q12–24h.
 - **Benazepril:** 0.25 mg/kg PO q12–24h.

Nutrition \$-\$\$

Nutrition is a very important factor in any case of acute kidney failure. These patients are usually in a catabolic state for many reasons. Counteracting this state with adequate calorie administration is vital to recovery. Many patients are anorectic during the severe uremia stage, necessitating the use of feeding tubes or parenteral nutrition. A prescription renal diet that is low in phosphorus and protein is recommended. Voluntary feeding can be stimulated with other foods. However, as soon as the appetite has recovered, the diet should be switched to a primarily renal diet.

Omega-3 Fatty Acids \$

Believed to help slow the progression of chronic kidney disease, this nutritional supplement may help protect the renal tubular cells from continued damage in cases of acute kidney failure. Many formulations are available, and the labeled dosage is recommended. Fatty acids are also a component of several of the prescription kidney diets; if a dog is fed this type of food, additional supplementation is unnecessary.

Patient Monitoring

- Vital signs as well as blood pressure should be monitored several times throughout the day, more frequently in patients that are less stable.
- Serum creatinine, BUN, and phosphorus levels should be checked every 1 to 2 days to monitor for changes. Electrolytes should be checked daily.
- CVP and urine output should be checked frequently in critical patients. As urine output starts to decrease, these values may need to be checked hourly to determine if therapeutic changes are needed.
- Patients should be weighed once to twice a day to keep track of weight loss from anorexia and increased catabolism and to get an idea of their hydration status (1 kg body weight = 1 L of fluid).

Home Management

- After these patients leave the hospital, follow-up is vital. They should return at least weekly in the beginning for monitoring of blood work, blood pressure, and weight to assess their progress. Additionally, pet owners should be educated about the situation, including what signs of problems they should look for at home. Clients should also be educated about keeping the pet away from similar situations in the future.
- Plenty of clean, fresh water should be available at all times.
- Fluid administration may be continued at home via the enteric route if a feeding tube is in place or with SC fluids administered daily to once every few days.
- These patients typically exhibit polydipsia and polyuria as their kidneys continue to recover and may need to be let outside more often to urinate.
- A prescription diet specifically designed for kidney patients is recommended. Specific energy requirements should be calculated using the formula $\text{Kcal} = (\text{Weight in kg} \times 30) + 70$. The amount of food that needs to be fed to fulfill this requirement is then figured out based on kcal per cup or can. This amount of food needs to be either administered through a feeding tube or voluntarily eaten each day.

Milestones/Recovery Time Frames

- If a patient does not develop azotemia within 72 hours of ingesting grapes or raisins, it is likely that any clinical problems will be avoided.
- As kidney function recovers, patients move from being oliguric or anuric to polyuric. This polyuric recovery stage may last from weeks to months.

- Kidney enzymes do not usually return to normal levels for some time after discharge. They should, however, stabilize at some value at which the animal is not clinically ill. Blood work values may never return to normal or may take weeks to months to do so as the kidneys recover.

Treatment Contraindications

- Potentially nephrotoxic drugs (e.g., aminoglycoside antibiotics, NSAIDs) should be avoided.
- If the patient is anesthetized for a kidney biopsy, blood pressure needs to be closely monitored and every precaution taken to avoid hypotension. Anesthesia may reduce blood flow to the kidneys and potentiate the damage caused by the grapes and raisins. Benefits of anesthesia versus risks must be carefully weighed.
- Epatikin contains calcium carbonate and chitosan, so it cannot be given in animals that are hypercalcemic.

PROGNOSIS

Favorable Criteria

- Early onset of therapy.
- Continued adequate urine output (1–2 ml/kg/day).
- Voluntary eating.
- Response to therapy within 7 to 10 days.
- Intact basement membrane on histopathology.

Unfavorable Criteria

- Delayed onset of treatment.
- High initial calcium level.
- Ataxia or weakness.
- Decreased or absent urine output.
- Clinical deterioration despite aggressive therapy.
- Injury to basement membrane on histopathology.

RECOMMENDED READING

- Eubig PA, Brady MS, Gwaltney-Brant SM, et al: Acute renal failure in dogs after the ingestion of grapes or raisins: A retrospective evaluation of 43 dogs (1992–2002). *J Vet Intern Med* 19(5):663–674, 2005.
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