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CASE SERIES

Acute kidney injury in dogs following ingestion of cream of tartar and tamarinds and the connection to tartaric acid as the proposed toxic principle in grapes and raisins

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Abstract

Objective: To (1) describe exposure history, clinical signs, treatment, and diagnostic findings in 4 dogs following ingestion of tamarinds, and in 2 dogs following ingestion of cream of tartar, and (2) discuss tartaric acid, the common denominator, as the proposed toxic principle in tamarinds and grapes.

Series Summary: Reports in which dogs developed acute kidney injury following ingestion of cream of tartar or tamarinds were identified from the ASPCA Animal Poison Control Center electronic database. In these cases, decontamination was not performed, and treatments were delayed. Despite IV fluids and symptomatic and supportive care, 2 of the dogs became anuric and 1 became oliguric. Four dogs were euthanized, and the outcome is unknown for 2 of the dogs. Necropsies were performed on 3 of the dogs. Clinical signs, laboratory findings, and histopathologic lesions were similar to those reported in grape and raisin toxicosis.

New or Unique Information Provided: Acute kidney injury may develop following ingestion of cream of tartar or tamarinds in dogs. Connecting these reports with findings in grape and raisin toxicosis and the sensitivity to tartaric acid in dogs, tartaric acid is identified as the likely toxic component in grapes and tamarinds.

KEYWORDS
AKI, canine, nephrotoxins, *Vitis vinifera* ingestion

1 | INTRODUCTION

Tartaric acid is an organic acid found in a variety of plants with the highest concentrations in grapes and tamarinds.[1] The concentration of tartaric acid depends on a variety of factors such as genotype or cultivar of the fruit, growing conditions, and locality.[1–5] Tamarind pulp contains a general range of 8%–18% tartaric acid.[5,6] Grapes are reported to contain as much as 2%, with a general range between 0.35% and 1.1%.[7] For comparison, other common fruits such as cherries and raspberries are reported to contain 0.008% and 0.009% tartaric acid, respectively.[1] In both grapes and tamarinds, the tartaric acid is present as free acid, the potassium bitartrate salt, and in lesser

Abbreviations: ACTH, adrenocorticotropic hormone; AKI, acute kidney injury; RI, reference interval; Tco_2, total carbon dioxide.

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amounts as calcium tartrate.[6,8] In grapes, during the ripening process, an increased proportion of tartaric acid is precipitated into salts such as potassium bitartrate.[3,9]

In this report, we describe a series of cases reported to an animal poison control center[a] in which vomiting and acute kidney injury (AKI) developed in dogs after exposures to tamarinds and cream of tartar (potassium bitartrate). Connecting this novel information with the reported sensitivity to tartaric acid in dogs, we explore the theory that tartaric acid and its salts are the toxic components in grapes and tamarinds.

2 | CASE 1

A 5-year-old, 28-kg previously healthy male neutered, mixed breed dog presented to a veterinary hospital for acute uncontrolled vomiting, weakness, and staggering for the previous 24 hours. Approximately, 24 hours prior to presentation the dog ingested 4 cups of homemade play dough containing 13.52 g (4 tsp) of cream of tartar (483 mg/kg). Vomiting began within 1–2 hours of ingestion and persisted every 30 minutes for the next 12 hours. Neurological changes began with ataxia at home that progressively worsened starting approximately 18 hours after ingestion. At the hospital, the patient was recumbent, not responsive to noxious stimuli, had cold extremities, no reaction to distal limb deep pain stimulus, no menace response OU, and anal sphincter tone was weak. Blood work at presentation showed renal azotemia with a creatinine of 751.5 μmol/L (reference interval [RI], 20–150 μmol/L) (8.5 mg/dl [RI, 0.5–1.8 mg/dl]), BUN 23.2 mmol/L (RI, 2.5–9.6 mmol/L) (65 mg/dl [RI, 7–27 mg/dl]), normal electrolytes, and a urine specific gravity of 1.012. Poison control was contacted, and aggressive supportive care was instituted for AKI of unknown cause. The dog was administered an IV bolus of 400 ml Lactated Ringer's solution and then administered 200 ml/h of Lactated Ringer's solution as a continuous infusion. Additional treatments included maropitant 1 mg/kg IV, famotidine 1 mg/kg IV, ondansetron 0.5 mg/kg IV, and a 60-ml warm water enema to evacuate potential remaining play dough from the colon. Six hours after presentation, the creatinine and BUN mildly worsened (786.9 μmol/L [8.9 mg/dl] and 26.4 mmol/L [74 mg/dl], respectively), and the dog was noted to have relative oliguria. The dog's sodium was 150 mmol/L at presentation (RI, 144–160 mmol/L) and since hypernatremia is often a concern following ingestion of homemade play dough ingestion, the sodium was confirmed normal at the 6-hour recheck (149 mmol/L). The play dough recipe in this case uniquely contained only a small amount (1 tsp or about 5.9 g) of sodium chloride. Overnight care was continued at a 24-hour emergency and specialty hospital where an ACTH stimulation test was performed, and radiographs revealed mild peritoneal effusion. After samples were obtained, dexamethasone 0.2 mg/kg IV was administered, and IV fluid therapy was continued.

Seventy-two hours after ingestion, the dog was dull and ataxic. The post-ACTH cortisol was 438.7 nmol/L (RI, 165.5–496.6 nmol/L) (15.9 μg/dL [RI, 6–18 μg/dL]), ruling out Addison's disease as a confounding factor. Approximately 96 hours after ingestion, the dog was euthanized due to reactive, generalized seizures and a necropsy was performed.

Gross examination revealed peritoneal effusion, subcutaneous and gastric wall edema, and petechial and ecchymotic hemorrhages in the pericardium, urinary bladder mucosa, and intestine. Other gross findings observed included moderate gallbladder biliary sludge and bile stasis. The most relevant histopathologic findings were severe renal tubular degeneration and necrosis with multifocal tubular mineralization, fibrinoid vascular necrosis with neutrophilic vasculitis in the gastrointestinal tract, urinary bladder, heart, and brain, and pulmonary edema.

3 | CASE 2

An 11-year-old, 9.6-kg male neutered miniature dachshund developed vomiting within 1–2 hours after an observed ingestion of 6.76 g (2 tsp) of cream of tartar (704 mg/kg of potassium bitartrate). The vomiting continued and the dog presented to a veterinary hospital about 30 hours postexposure. At presentation, the dog's creatinine was 521.7 μmol/L (RI, 44.2–159.1 μmol/L) (5.9 mg/dl [RI, 0.5–1.8 mg/dL]) and the BUN was 26.4 mmol/L (RI, 2.1–8.9 mmol/L) (74 mg/dL [RI, 6–25 mg/dL]) with a urine specific gravity of 1.008. Diagnostic evaluation and symptomatic care were recommended, and the outcome of the case is unknown.

4 | CASE 3

A 6.5-year-old, 28-kg previously healthy female intact bull terrier presented to a veterinary emergency clinic for vomiting and diarrhea. Two days prior (approximately 53 h before presentation), the dog ingested 6–7 tamarind pods. Vomiting developed 14 hours postexposure and no treatments were done prior to presentation. Significant abnormalities were noted on the biochemistry panel, including creatinine of 875.4 μmol/L (RI, 44.2–159.1 μmol/L) (9.9 mg/dL [RI, 0.5–1.8 mg/dL]), BUN of 40.7 mmol/L (RI, 2.1–8.9 mmol/L) (114 mg/dL [RI, 6–25 mg/dL]), calcium 3.92 mmol/L (RI, 2.22–2.84 mmol/L) (15.7 mg/dL [RI, 8.9–11.4 mg/dL]), and phosphorus 3.42 mmol/L (RI, 0.81–1.94 mmol/L) (10.6 mg/dL [RI, 2.5–6.0 mg/dl]). Symptomatic care was recommended, and the outcome of the case is unknown.

5 | CASE 4

A 6-year-old, 11.3-kg neutered male miniature dachshund with a history of back pain developed vomiting, depression, and polydipsia within 2 hours after ingesting approximately 80 g (0.5 cup) of tamarind paste. Tamarind was noted in the vomitus. Initial treatment was withholding food and water at home followed by outpatient care at an emergency hospital. About 30 hours after the exposure, the

dog returned to the emergency hospital and was dehydrated and had some abdominal pain. Laboratory work performed at 43 hours postexposure revealed azotemia with creatinine of 362.5 μmol/L (RI, 44.2–159.1 μmol/L) (4.1 mg/dl [RI, 0.5–1.8 mg/dL]), BUN of 28.2 mmol/L (RI, 2.1–8.9 mmol/L) (79 mg/dL [RI, 6–25 mg/dL]), phosphorus of 3.55 mmol/L (RI, 0.81–1.94 mmol/L) (11 mg/dl [RI, 2.5–6.0 mg/dL]), and calcium 2.79 mmol/L (RI, 2.22–2.84 mmol/L) (11.2 mg/dL [RI, 8.9–11.4 mg/dL]). Blood pH was 7.26 (RI, 7.31–7.42). Further diagnostics and symptomatic care were recommended. Upon follow-up, the owner reported that the dog was euthanized 5 days postexposure due to AKI.

6 | CASES 5 AND 6

Two previously healthy French bulldogs, a 2-year-old neutered male weighing 9.2 kg and a 2-year-old neutered male weighing 13.3 kg, ingested an estimated 14–28 g (0.5–1 oz) of tamarind paste from a 454 g (1 lb) bag. Polydipsia, trembling, and severe vomiting were reported within 12 hours. Tamarind paste was noted in the vomitus. About 32 hours postexposure, the dogs were found to be significantly azotemic with creatinine values of 483 μmol/L (RI, 44–159 μmol/L) (5.46 mg/dL [RI, 0.5–1.8 mg/dL]) and 663 μmol/L (7.5 mg/dL) and BUN of 21.9 mmol/L (RI, 2.5–9.6 mmol/L) (61 mg/dL [RI, 6–25 mg/dL]) and 23.6 mmol/L (RI, 2.5–9.6 mmol/L) (66 mg/dL [RI, 6–25 mg/dL]), respectively. Initial treatment consisted of IV fluids, antacids, antiemetics, analgesics, and antimicrobials (for suspected aspiration pneumonia). The next day, the dogs were referred to a veterinary teaching hospital for continued care. Despite furosemide and continued IV fluids, their creatinine values increased to 681 μmol/L (RI, 20–150 μmol/L) and 695 μmol/L (7.7 and 7.86 mg/dL), respectively, and they became anuric. Both dogs were also hypercalcemic and hyperphosphatemic with calcium values of 4.05 mmol/L (RI, 2.5–3.00 mmol/L) and 3.63 mmol/L and phosphorus values of 3.69 mmol/L (RI, 0.9–1.85 mmol/L) and 3.24 mmol/L, respectively. Other notable laboratory changes included increased anion gaps of 53 mmol/L (RI, 13–24 mmol/L) and 45 mmol/L and low total carbon dioxide (TCO_2) values of 10 mmol/L (RI, 15–25 mmol/L) and 11 mmol/L. Urinalysis was performed in the 9.2 kg dog and results showed a pH of 7.5, specific gravity of 1.009, 1+ glucose, 2+ protein, 3+ blood, 2–5 leukocytes/400×, 5–10 transitional epithelial cells/400×, and occasional bacteria. Microscopic agglutination test antibody titers for Leptospirosis were reported for the 13.3-kg dog and showed less than 100 (negative) for all serovars tested except for *Leptospira bratislava*, which was reported at 100. Both dogs had been vaccinated for Leptospirosis 8–9 months prior.

Both dogs were euthanized, and necropsies were performed. Renal histopathologic findings were similar for both dogs and included tubules lined by swollen and vacuolated or shrunken and hypereosinophilic epithelial cells and occasional intraluminal casts of sloughed epithelial cells mixed with necrotic debris. These changes were interpreted as acute severe cortical tubular degeneration and necrosis, suggestive of exposure to a nephrotoxin.

7 | DISCUSSION

Tartaric acid and its salts are used in pharmaceuticals, cosmetics, food additives, baked goods, and some homemade playdough recipes. Cream of tartar is a potassium salt of tartaric acid and is harvested as a by-product of winemaking. Tartrates are often removed (detartrated) from commercial products such as grape juice, jam, and wine.[8]

Species differences in tartaric acid absorption, elimination, and toxicity have been documented. Absorption in people is thought to be low due to fermentation to short-chain fatty acids by colonic bacteria,[10] though there is 1 report[11] of hyperkalemia in 2 people following large ingestions of cream of tartar. Dogs are a species with unique sensitivity to tartaric acid [12–14] as well as other organic acids, such as maleic acid.[15,16] In a case report of 3 dogs exposed to a descaling product containing maleic acid, severe vomiting followed by AKI was reported.[15] Renal histological changes revealed acute proximal tubular necrosis that was consistent with toxic nephropathy.[15]

The absorption, elimination, and effects of tartaric acid in dogs have been described in multiple older laboratory studies. Tartrates were shown to be excreted in the urine almost quantitatively at sub-nephrotoxic dosages following oral and subcutaneous administration.[12] Another study correlated the toxicity of tartaric acid with the high rate of renal excretion in dogs, with 50% of the administered dose recovered in urine within 12 hours.[14] Experimentally, the characteristic lesion in dogs and rabbits is extensive necrosis of the convoluted tubules.[12,13,17] In dogs, an acute oral dosage of sodium potassium tartrate (also known as Rochelle salt) as low as 400 mg/kg resulted in tubular necrosis, with more consistent renal changes noted at 600 mg/kg and above.[12] In another dated study,[18] 4 dogs were given 990 mg/kg/day tartaric acid (divided into 2 doses 6 h apart, stereoisomer not specified) for 90–114 days. Casts appeared in the urine of 3 dogs and 1 dog became azotemic at day 88 and died at day 90. Renal histopathology revealed advanced tubular degeneration. Toxicity of potassium bitartrate salt (also known as potassium hydrogen tartrate or cream of tartar) in dogs has not been evaluated, to our knowledge. One report in rats describes obstructive nephropathy following exposure to DL-potassium hydrogen tartrate.[19]

It is worth noting that experiments in rabbits found that at low dosages, there was significant individual variation in response to tartrates.[12,17] When there was a response at lower dosages, the degree and type of renal lesions were comparable to higher dosages. While large dosages invariably caused marked effects, the authors noted that there was not a direct correlation between dosage and degree of renal damage.[17] Investigations into variables that may affect nephrotoxicity have included fasted versus fed states, alkalinization, and high-calcium diets.[12,17] Although the well-fed state and alkalinization showed slight protection from tartrate-induced nephrotoxicity, the differences were minor.[17]

The mechanism by which tartaric acid causes renal tubular necrosis was not described in the literature. Maleic acid, which has been reported to cause similar lesions in dogs, is thought to selectively inhibit NaK-ATPase activity[20] and/or deplete ATP[21] in the proximal tubules. It is possible that tartaric acid has similar mechanisms.

Other toxicologic causes of AKI in dogs include grapes and raisins, ethylene glycol, cholecalciferol, and heavy metals.[22] Exposure to medications such as aminoglycoside antibiotics, amphotericin B, cisplatin, and nonsteroidal anti-inflammatory drugs may also lead to AKI.[22] Infectious causes include leptospirosis and pyelonephritis.[22] AKI may also occur secondary to ischemia, infarction, acute pancreatitis, sepsis, hyperviscosity, multiple organ dysfunction syndrome, and hemoglobinuria/myoglobinuria.[22] In the cases described in this report, exposure certainty was high (either observed or with strong evidence of exposure such as chewed material or packaging or material present in the vomitus). There was no evidence of exposure to other nephrotoxins, and other etiologies were not evident.

In 2001, the first report of AKI in dogs following ingestions of grapes and raisins was published.[23] In 2005, Eubig et al. published a retrospective evaluation of cases of acute renal failure in 43 dogs following exposure to grapes and raisins.[24] The report discusses clinical signs, clinicopathologic findings, prognostic indicators, and histopathologic findings. The evaluation found that vomiting was the most common clinical sign (100% of dogs), followed by lethargy, anorexia, diarrhea, decreased urine output, and abdominal pain. Ataxia and weakness were reported in 23% and 19% of the dogs, respectively. In addition to azotemia, the evaluation also noted that the majority of the dogs developed hypercalcemia and hyperphosphatemia, with higher median Ca × P products in dogs that were euthanized or died compared to dogs that survived. Lower TCO_2 was also noted in dogs that did not survive. In this same study, ataxia and weakness were associated with lower survival. The authors did not find a relationship between survival and dosage of grapes or raisins ingested and noted that AKI does not consistently develop at dosages similar to or higher than those described in the report. In an effort to identify the toxic principle, leftover grapes and raisins were screened for pesticides and mycotoxins and none were detected. Herbicide screening was performed on 1 dog's liver and there were none detected. Quantification of 25-(OH)D3 (calcifediol) on renal and hepatic specimens was unremarkable.

Schweighauser et al compared neurologic signs in dogs with AKI from grape and raisin toxicosis to dogs with AKI from other causes.[25] They found that neurological signs associated with grape and raisin toxicosis are an important feature and seem to be reversible and are not correlated with degree of uremia, systemic hypertension, electrolyte disorders, or other metabolic derangements. They also noted that the neurologic signs were not associated with structural brain changes. Similar to earlier reports, they also found statistically significant hypercalcemia and further noted that in their study, it was limited to total calcium and not the ionized fraction and suggested that the calcium may be complexed to an unknown anion not reflected in the anion gap.

Histopathology in dogs following grape and raisin ingestions is described in several reports. The most consistent lesion was moderate to severe, diffuse renal tubular degeneration, especially in the proximal tubules. Proteinaceous and cellular debris was noted in some tubule lumens. Mineralization of necrotic cells and tubular basement membranes in the kidney has also been described.[24–26] Extrarenal lesions associated with renal failure, such as fibrinoid vascular necrosis and soft tissue mineralization, have also been described.[24]

Gross and histopathologic changes described in cases of grape and raisin intoxication closely resemble the features of tamarind and tartaric acid poisoning in dogs. The central histologic change shared by all cases is a severe and diffuse acute renal tubular degeneration and necrosis, predominantly affecting the proximal convoluted tubules and sometimes accompanied by renal tubular or basement membrane mineralization.

The cases in this report describe clinical signs, laboratory findings, and histopathologic lesions in dogs exposed to tamarinds and potassium bitartrate that are similar to those described in grape and raisin toxicosis dogs. Considering tartaric acid, a demonstrated nephrotoxin in dogs, as the common denominator, it is likely that tartaric acid and its salts are responsible for nephrotoxicity in dogs following exposure to these agents. The published grape and raisin dosages that have led to AKI in dogs are consistent with potential nephrotoxic concentrations of tartaric acid.[b]

Although variable concentrations of tartaric acid may, in part, explain inconsistent toxicity following similar ingested amounts of grapes and raisins, there may also be individual variation or circumstances that influence individual sensitivity as was noted in early tartaric acid studies.[12,17] Detartration of processed products could explain the lack of reported toxicosis following exposure to agents such as grape juice, jam, and wine. Thermal decomposition of tartaric acid may explain the anecdotal observation that cooked grapes and raisins are less likely to be implicated in cases of AKI (ASPCA Animal Poison Center Database: Unpublished data, 2002–2021). The exact temperature and duration of the heating process for full decomposition were not located in the literature.

Further work may explore the significance of hypercalcemia and hyperphosphatemia in these cases and the possible contribution of calcium tartrate. Since some of the tartaric acid gets eliminated in the urine as a parent compound, it might be possible to test the urine for the presence of tartrates, although it may not be possible to predict severity of clinical signs based on that level.

Treatment for dogs exposed to tamarinds or cream of tartar should include prompt emesis and aggressive fluid therapy. Blum et al. found gastric emptying of tartaric acid is delayed in dogs.[27] This may explain the anecdotal and published observations of prolonged retention of grapes and raisins in the stomach and recovery in emesis up to 8 and 13 hours for grapes and raisins, respectively.[28] Consistent with reports in grape and raisin toxicosis cases, spontaneous vomiting is common and may be an early indicator of toxicosis. Currently, the efficacy of activated charcoal for tartaric acid is unknown. Given the clinical presentation of the cases in this report, it is reasonable to expect spontaneous vomiting within 12–24 hours and azotemia within 24–48 hours postexposure.

In the cases described in this report, decontamination was not performed, and treatments were delayed. Despite IV fluids and symptomatic and supportive care, 2 of the dogs became anuric and 1 was oliguric. Four of the dogs were euthanized and the outcome is unknown for 2 of the dogs. Awareness of the potential toxicity of cream of tartar and tamarinds in dogs will allow for prompt decontamination and proactive IV fluid diuresis, which could lead to improved outcomes. In

addition, recognizing tartaric acid as the potential nephrotoxic component in grapes and raisins may enable advancements in research, diagnostics, and treatment of grape and raisin toxicosis in dogs.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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ENDNOTES

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