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ORIGINAL ARTICLE

Incidence of *Vitis* fruit-induced clinical signs and acute kidney injury in dogs and cats

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Objectives: To determine the incidence of clinical signs and *Vitis* fruit-induced acute kidney injury in dogs and cats with a *Vitis* fruit ingestion reported to the Dutch Poisons Information Center, and a description of the therapies instituted by the veterinarians.

Materials and Methods: All cases of *Vitis* fruit ingestions in dogs and cats reported to the center between January 1, 2018 and December 31, 2018 were included in this study. Veterinarians and pet owners were contacted by phone or email to obtain follow-up information. Information was collected using a standardised data collection sheet.

Results: Ninety-five dogs and 13 cats with proven *Vitis* fruit ingestion were included. Fourteen dogs and two cats developed clinical signs: emesis (11/16, 68.8%), lethargy (5/16, 31.3%), diarrhoea (3/16, 18.8%), anorexia (3/16, 18.8%), tremor (2/16, 12.5%) and restlessness (1/16, 6.3%). The overall incidence for developing clinical signs was 14.7% in dogs and 15.4% in cats. One (1/95, 1%) dog developed acute kidney injury after ingestion of *Vitis* fruit. No cats developed acute kidney injury. Induction of emesis and/or administration of activated charcoal was instituted in 72 of 82 (88%) and eight of 11 (73%) of asymptomatic dogs and cats and six of 14 (43%) and two of two (100%) of symptomatic dogs and cats, respectively. Overall, emesis was induced in 72 of 95 (76%) dogs (100% success rate) and removed *Vitis* fruits in the majority of cases (98% when induced <4 hours after ingestion and 83% when induced 4 to 12 hours after ingestion). Emesis was induced in seven of 13 (54%) cats (86% success rate) and removed *Vitis* fruits in 83% of the cases.

Clinical Significance: In this study, a significant proportion (around 15%) of dogs and cats developed clinical signs after ingestion of *Vitis* fruits, which were predominantly related to the gastrointestinal tract. Symptomatic acute kidney injury was rare. Our findings suggest the use of decontamination measures, *i.e.* induction of emesis, may be warranted up to 12 hours after ingestion.

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INTRODUCTION

In 2001, the Animal Poison Control Center of the American Society for the Prevention of Cruelty to Animals alerted the veterinary community concerning an association between the ingestion of the fruits of *Vitis vinifera* (grapes, raisins, currants and sultanas) and acute kidney injury (AKI) in dogs (Gwaltney-Brant *et al.* 2001). After this publication, several case series emerged in the veterinary literature confirming this finding (Mazzaferro *et al.* 2004, Eubig *et al.* 2005, Sutton *et al.* 2009, Reich *et al.* 2020, Croft *et al.* 2021).

Based on the available data, there is a strong suggestion that in dogs, AKI can develop after ingestion of grapes, raisins, currants and other food products containing *Vitis* fruits.

No dose–response relationship appears to be present as ingestion of four to five grapes was sufficient to induce AKI in a dachshund (Mazzaferro *et al.* 2004), while other dogs remain asymptomatic after ingestion of raisins up to 1 kg (Sutton *et al.* 2009). The pathogenesis of *Vitis* fruit toxicity is not known. Recently, tartaric acid and its salt, potassium bitartrate, are proposed as toxic agents in grapes leading to AKI in dogs (Wegenast *et al.* 2021). Other suggested hypotheses are carnivore-related factors like the intolerance to tannins and flavinoids or the excessive ingestion of monosaccharides (Singleton 2001) and contamination with unknown toxin(s) or environmental toxins, *e.g.* mould toxins, pesticides, heavy metals, but none has been proven yet (Gwaltney-Brant *et al.* 2001, Croft *et al.* 2021).

Most dogs that get sick after ingestion of *Vitis* fruits will start to show clinical signs within 24 hours. Signs consist of vomiting, diarrhoea, lethargy and anorexia, followed by polydipsia, polyuria or decreased urine output (oliguria to anuria), ataxia, abdominal pain and lethargy in second instance. Biochemical markers of AKI are present 24 to 48 hours after ingestion and include elevated blood creatinine and urea concentrations, and proteinuria (Gwaltney-Brant *et al.* 2001, Mazzaferro *et al.* 2004, Eubig *et al.* 2005). In cases with severe AKI, neurological signs have been reported as common (Schweighauser *et al.* 2020). At the moment, it is recommended to treat all dogs that ingested *Vitis* fruits aggressively even if small amounts have been ingested. Decontamination measures, *e.g.* emesis, lavage and the administration of activated charcoal are advised after recent ingestion, followed by intravenous fluid diuresis for at least 48 hours. Serum chemistry values should be monitored for 72 hours for the development of AKI (Gwaltney-Brant *et al.* 2001, Eubig *et al.* 2005, Campbell 2007, Sutton *et al.* 2009). If symptoms related to AKI develop, treatment is extended to reduce its impact.

Whether cats develop AKI or other clinical signs after the ingestion of *Vitis* fruits is still not clear. A publication by the Veterinary Poisons Information Service in the UK mentioned the development of acute renal failure in two cats after the ingestion of *Vitis* fruits (Sutton *et al.* 2009). MEDLINE (PubMed) has been searched for articles in the English language with the following keywords *Vitis* fruits (grapes, raisins, currants and sultanas) and cats on October 1, 2021. No other reports on *Vitis* fruit ingestions in cats have been found doing these searches.

Veterinarians and pet owners are becoming more and more aware of the potential danger of *Vitis* fruits and information requests made to the Dutch Poisons Information Center (DPIC) by veterinarians concerning dogs and cats exposed to *Vitis* fruits are increasing (Fig 1). The increasing number of reported cases of *Vitis* fruit ingestion to the DPIC is associated with a significant increase in veterinary care consumption. The above mentioned contemporary guidelines suggest a relatively time-consuming, intense and potentially expensive treatment. To justify such an approach, it is necessary to critically appraise the potential health risk of *Vitis* fruits. Unfortunately, current information on the incidence of AKI after *Vitis* fruit ingestion is limited (Eubig *et al.* 2005, Sutton *et al.* 2009, Reich *et al.* 2020, Croft *et al.* 2021).

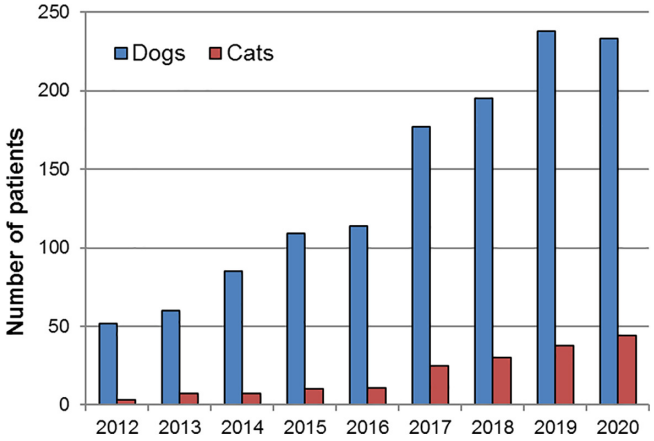

FIG 1. Number of patients related to information requests made to the Dutch Poisons Information Center (DPIC) by Dutch veterinarians concerning dogs and cats exposed to *Vitis* fruits per year

Therefore, the aim of this prospective, surveillance study was to determine the incidence of clinical signs and *Vitis* fruit-induced AKI in dogs and cats with a *Vitis* fruit ingestion reported to the DPIC, and a description of the therapies instituted by the veterinarians who contacted the DPIC for information.

MATERIALS AND METHODS

All cases concerning *Vitis* fruit ingestions in dogs and cats reported to the DPIC between January 1, 2018 and December 31, 2018 were included. Cases concerning animals exposed to other *Vitis* plant materials, *e.g.* roots and leaves, and co-ingestions with other toxic substances were excluded. During the study, veterinarians with an information request on *Vitis* fruit ingestion were approached by the DPIC representative after the standard communication protocol of the centre had been finalised. This protocol includes sharing information on the potential health impact of *Vitis* fruit ingestion and on general treatment guidelines as recommended at the time of the study, *i.e.* gastric decontamination (emesis or gastric lavage) and activated charcoal after all recent ingestions (<4 hours, irrespective of the amount ingested) followed by intravenous fluid diuresis (~4 to 5 ml/kg/hour of a balanced isotonic crystalloid) for at least 48 hours. As part of the protocol, it was advised to monitor renal function such as serum urea and creatinine on a daily basis for 3 days. The contacting veterinarians were informed on the study and participation was requested by the DPIC representative (oral informed consent). Approximately 1 week after contact with the DPIC, the veterinarians were approached by phone or email. Subsequently, animal owners were contacted by the veterinarian who initially contacted the DPIC or directly by one of the authors after obtaining informed consent via the inquiring veterinarian. Both from veterinarians and owners, information was collected using a standardised data collection sheet (Table 1).

Dogs and cats with witnessed ingestion or that had *Vitis* fruits in their vomitus or stool and from which complete data could be obtained were included for further analysis. Patients with suspected or known renal disease in their medical history, clinical

signs deemed likely to be caused by concurrent disease or a recent history of treatment with nephrotoxic medication were excluded, with the exception of non-steroidal anti-inflammatory drugs (NSAIDs). Many dogs are on chronic NSAID treatment due to a range of chronic diseases such as arthrosis and represent an important group within the patient population visiting a first-opinion practice. The development of AKI was determined based on clinical signs, *i.e.* anorexia, vomiting, diarrhoea and lethargy, for more than 24 hours in combination with blood urea (BUN) and creatinine concentrations. We applied the following reference values: BUN 3.0 to 12.5 mmol/L (dog), 6 to 12.8 mmol/L (cat); and creatinine 50 to 129 µmol/L (dog), 76 to 164 µmol/L (cat) as a general indicator to distinguish normal from abnormal values in case the original reference range was unknown.

Results are presented using descriptive statistics and data as median (range) if not stated otherwise.

This study was merely observational and no study-related intervention was imposed upon the animals. Therefore, our institution deemed that ethical approval was not required.

RESULTS

In 2018, the DPIC received 231 information requests by telephone concerning *Vitis* fruit ingestion by dogs (n=197), cats (n=33) and rabbit (n=1). After application of the inclusion and exclusion criteria, 95 dogs (48%) and 13 cats (40%) remained for further analysis (Fig 2). The analysed data set is compiled of three sources; information obtained from the written report from the initial contact, telephone contact with the inquiring veterinarian approximately 1 week after the initial contact and follow-up performed by contacting the owners, respectively, 9 (5–21) days and 9 (6–16) days after the ingestion of *Vitis* fruit in dogs and cats.

Dogs

The most common breeds were mixed breed (n=27/95), Labrador retriever (n=10/95) and beagle (n=7/96). Forty-two other breeds comprised the remaining 51 (53%) dogs. The study population consisted of 32 (34%) entire females, 24 (25%) neutered males, 22 (23%) entire males and 17 (18%) neutered females. The age was 2.0 (0.17 to 11.0) years with a bodyweight of 16 (1.9–60.0) kg. Seventy dogs ingested *Vitis* fruit (70/95), *i.e.* raw fruits (grapes; n=48/70) and dried fruits (raisins and currants; n=22/70). Twenty-five dogs (25/95) ingested food products containing some form of *Vitis* fruits, like currant buns, apple pies and freshly made grape juice. The quantity of grapes ingested ranged from one grape to 1 kg per dog and for raisins and currants from one single piece to 250 g per dog. For *Vitis* fruit-containing food products, it was impossible to estimate the ingested amount of raisins and/or currants. Ten dogs had a medical history directly preceding the ingestion of *Vitis* fruits, all unrelated to renal disease. Four of these dogs received medication for these problems (Table 2).

Most dogs did not show any symptoms after ingestion of *Vitis* fruits (n=82/95; 86.3%). In 14 dogs, symptoms were noticed by their owners before visiting the veterinarian. Characteristics of these dogs are presented in Table 3. Dogs predominantly suffered from clinical signs related to the gastrointestinal tract. *Vitis* fruits were detected in spontaneously produced vomit (n=3/9) and diarrhoea (n=1/3).

During follow-up, by contacting the veterinarian approximately 1 week after the initial contact and follow-up by contacting the dog owner, with the exception of one dog, none of the dogs had developed a combination of clinical signs indicative of AKI, *i.e.* anorexia, vomiting, diarrhoea and lethargy for more than 24 hours. Three dogs had diarrhoea without vomiting. All three dogs were active and had a good appetite: in one dog, the diarrhoea started before eating grapes, one dog was diagnosed with giardiasis and the aetiology of the diarrhoea remained unknown in one dog.

Table 1. Collection sheet for data related to the patient, the *Vitis* fruit exposure, medical history and clinical course

Patient characteristics	Species
	Breed
	Gender
	Age
	Bodyweight
Exposure-related data	Confirmation of exposure
	Type of *Vitis* fruit ingested
	(Estimated) amount ingested
	Time between ingestion and presentation
Medical history shortly before ingestion	Clinical signs
	Diagnosis
	Medication
Clinical course and treatment	Clinical signs and symptoms after ingestion
	Biochemical analysis
	Treatment by veterinarian
	• Decontamination measures
	• Fluid therapy

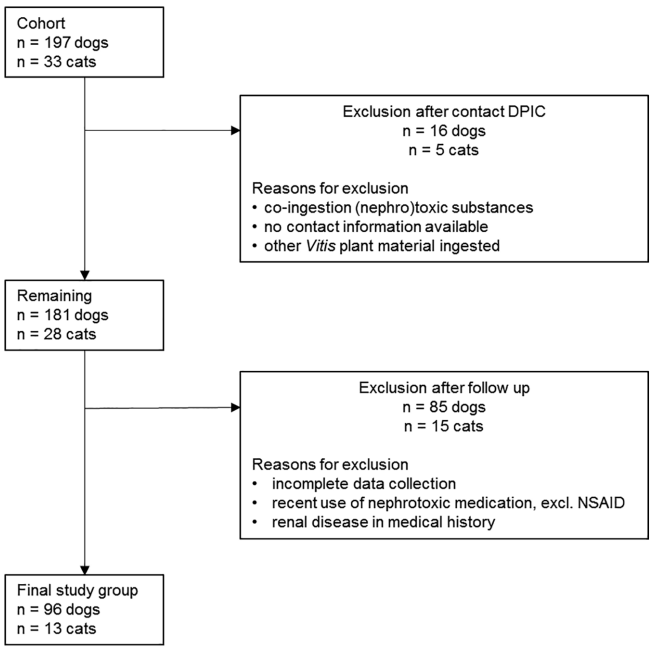

FIG 2. Stepwise exclusion chart for animals included in this study on *Vitis* fruit intoxication in dogs and cats

Biochemical analysis was performed in 29 dogs; in three dogs, serial analysis with an interval of 24 to 48 hours. Urea and creatinine concentrations were within the reference range, except for one dog that developed AKI (Table 3, dog no. 12); see case description.

Four dogs were treated according to the guidelines suggested by the DPIC, 83 dogs were treated partly according to the suggested guidelines and the owners of eight dogs did not present their dogs to the veterinarian. In the latter cases, the *Vitis* fruit ingestion was solely discussed during telephone contact, no treatment was instituted and none of these eight dogs did develop any clinical signs. One or more measures of decontamination were instituted in 78 of 95 dogs (82.1%); in 88% of the asymptomatic dogs 1.0 (0.5 to 36.0) hour after ingestion and in 43% of symptomatic dogs 2.5 (0.5 to 12.0) hours after ingestion (Tables 3 and 4). All dogs vomited after the induction of emesis with apomorphine. Sixteen dogs were treated with fluid therapy, one asymptomatic dog received subcutaneous fluid once and 10 asymptomatic dogs and five symptomatic dogs were given fluids intravenously (iv) (Table 5). On owner follow-up, all dogs except the dog with AKI, were in good health; polyuria and polydipsia were still present in the dog with AKI.

The dog with AKI, a mixed breed (Labrador retriever× Rottweiler) neutered female developed clinical signs of vomiting, anorexia and lethargy 3 days after ingestion of approximately 25 red grapes in a vineyard in the south of the Netherlands. At the time, the clinical signs were attributed to the external otitis and treatment of the otitis was started with topical ointment containing gentamicin. Five days after ingestion, the external ear canal was inspected under medetomidine/ketamine anaesthesia. No pre- or peri-anaesthetic fluids were administered. The next day, the dog developed diarrhoea while anorexia, vomiting and lethargy persisted. Nine days after ingestion, the dog remained

Table 2. Symptoms or diagnosis, and treatment preceding *Vitis* fruits ingestion by dogs

Symptoms or diagnosis	Number of dogs	Treatment
Diarrhoea†	1	–
Cough	1	–
Arthrosis	3	NSAID (in 2 dogs)
Pancreatitis‡	1	–
Otitis externa	1	–
Mammary gland tumours	1	NSAID after mastectomy§
Acute hepatitis¶	1	Dexamethasone
Epilepsy	1	–

†This dog vomited once with grapes in the vomitus
‡This dog was asymptomatic at the time of the *Vitis* fruits ingestion and continued to be asymptomatic after the ingestion of raisins
§Mastectomy was performed 10 days before ingestion of *Vitis* fruits
¶Acute hepatitis was diagnosed 10 days earlier and the dog was recovered by the time it ingested raisin buns. This dog was asymptomatic and continued to be asymptomatic after the *Vitis* fruit ingestion

Table 3. Characteristics of dogs and cats with clinical signs after *Vitis* fruit ingestion

	Signalment	*Vitis* fruits	Clinical sign	TTP	Treatment	Biochemistry†
Dog						
1	9 years, 26 kg Drents Partridge dog	Raisins 75 g	Restlessness	4 hours	F	BUN/urea: 5.8 Creatinine: 70
2	1 year 5 months, 26 kg Old English bulldog	Grapes 250 g	Diarrhoea, lethargy	10 hours	–	BUN/urea: 5.2 Creatinine: 70
3	4 years, 8.6 kg Pug	Raisins 200 g	Tremor	12 hours	E, F	BUN/urea: 1.8 Creatinine: 85
4	1 year 3 months, 14 kg Soft-coated Wheaten terrier	25 grapes	Emesis	0.5 hour	E	ND
5	9 years, 3.3 kg dachshund	25 raisins	Emesis	1 hour	E	ND
6	9 months, 10 kg Small Dutch Waterfowl Dog	15 grapes	Emesis, diarrhoea, lethargy	3 days	–	BUN/urea: 5.7 Creatinine: 68
7	10 years 9 months, 40 kg Hovawart	20 raisins	Emesis	24 hours	–	BUN/urea: 4.6 Creatinine: 54
8	11 months, 22 kg Australian shepherd	raisins 120 g	Lethargy	24 hours	–	BUN/urea: 5.7 Creatinine: 67
9	5 months, 16 kg Labradoodle	3 grapes	Emesis	1 hour	–	BUN/urea: 4.1 Creatinine: 56
10	5 months, 12 kg mixed breed	4 grapes	Emesis	3 hours	E, AC	ND
11	6 months, 9 kg beagle	5 grapes	Emesis, anorexia, lethargy	12 hours	F	BUN/urea: 3.6 Creatinine: 37
12	2 years 10 months, 34 kg mixed breed	25 grapes	Emesis, diarrhoea, anorexia	7 days	F	BUN/urea: 41.6 Creatinine: 1008
13	4 years 6 months, 1.9 kg Chihuahua	8 raisins	Tremor	2 hours	E	ND
14	5 years 6 months, 22 kg mixed breed	Grapes 500 g	Emesis	7 hours	AC	ND
Cat						
1	1 year, 5.2 kg domestic shorthair	Raisins 300 g	Emesis	2 hours	AC	BUN/urea: 8.0 Creatinine: 111
2	2 years 5 months, 2.4 kg domestic shorthair	10 raisins	Anorexia, lethargy	12 hours	AC	BUN/urea: 7.4 Creatinine: 115

TTP Time period from ingestion to presentation, F Intravenous fluid therapy, BUN Blood urea, E Emesis induced, AC Activated charcoal, ND Not determined
†Units in mmol/L (urea/BUN) and µmol/L (creatinine); urea reference value: 3.0 to 12.5 mmol/L (non-fasted dog), 6 to 12.8 mmol/L (cat); creatinine reference value: creatinine 50 to 129 µmol/L (dog), 76 to 164 µmol/L (cat)

sick and blood analysis demonstrated an increased plasma creatinine of 1008 µmol/L and BUN of 41 mmol/L. Fluid therapy (iv and subcutaneously) and antiemetics were given during 10 days. Gradually after 16 days, creatinine decreased to 184 µmol/L and BUN to 6.7 mmol/L. During the last follow-up, 37 days after ingestion, the specific gravity of the urine was 1.014 and the owner still noticed polyuria and polydipsia. No additional biochemical analysis was performed. This case illustrates the complexity to establish a relationship between *Vitis* ingestion and AKI as cases often are complicated by interfering diseases and treatments.

Cats

Thirteen cats fitting inclusion criteria were enrolled in this study (Fig 2). Domestic shorthairs were most common (n=10/13), complemented by one Persian cat (1/13), one Sphynx (n=1/13) and one Ragdoll (n=1/13). The sex distribution was seven male and six female cats, all neutered. The age was 1.4 (0.3 to 10.7) years and the weight was 3.7 (2 to 5.2) kg. None of the cats had any relevant medical history or use of medication before the ingestion of *Vitis* fruits. Two cats ingested, respectively, a quarter of a grape and one whole grape. The remaining 11 cats ate raisins or currants; the amount ranged from one raisin to 300 g of raisins. The cat eating 300 g of raisins was familiar with pica behaviour. Two cats showed symptoms after ingestion (2/13; 15.4%, Table 3). One cat vomited with raisins present in the vomitus and one cat was anorexic for 12 hours.

Biochemical analyses, including BUN and creatinine concentrations, were performed in six cats (no serial analysis) and none of the results were above the upper limit of the reference range.

One cat was treated according to the guidelines suggested by the DPIC, five cats were treated partly according to the suggested guidelines and the owner of one cat solely contacted the veterinarian by telephone to discuss the *Vitis* fruit ingestion. No treatment was applied and these cats remained asymptomatic. One or more measures of decontamination were instituted in 10 of 13 cats (77%); in 73% of the asymptomatic cats 1 (0.5–3.0) hour after ingestion and in 100% of symptomatic cats 2.5 and 12 hours after ingestion (Table 4). Emesis was induced in seven cats by administering an α_2-agonist (*e.g.* xylazine or medetomidine) with a success rate of 86% (6/7). Two cats were treated with fluid therapy, one received subcutaneous fluids once and the other cat was given fluids iv for 48 hours. According to follow-up given by the owners, all cats were in good health.

Table 4. Overview of gastrointestinal decontamination performed in dogs and cats

	Number of dogs (n=95)	Number of cats (n=13)
Decontamination	78	10
Emesis	45	3
<4 hours	42 (41)†	3 (3)†
4 to 12 hours	3 (3)†	
Emesis + activated charcoal	27	4
<4 hours	24 (24)†	4 (2)†
4 to 12 hours	3 (2)†	–
Activated charcoal	6	3
None	17	3

†The number of dogs and cats with remnants present in vomitus are given in parentheses

DISCUSSION

Ingestion of *Vitis* fruits, *i.e.* grapes and raisins/currants and food products containing some form of *Vitis* fruits, is quite common in dogs. Veterinarians and pet owners are nowadays becoming more aware of the potential dangers related to ingestion of *Vitis* fruits. To justify the current time-consuming, intense and potentially expensive treatment guidelines, more information concerning the incidence of *Vitis* fruit-induced clinical signs and *Vitis* fruit-induced AKI in dogs and cats is needed. In this prospective

Table 5. Overview of incidence's of *Vitis* fruit-induced clinical signs and acute kidney injury and applied treatment in dogs

	This study	Eubig *et al.* (2005)	Sutton *et al.* (2009)	Reich *et al.* (2020)	Croft *et al.* (2021)
Study type	Prospective surveillance study	Retrospective evaluation database	Retrospective evaluation database	Retrospective evaluation database	Retrospective evaluation database
Data source	PIC/DPIC	PIC/ASPCA	PIC/VPIS	3 university veterinary teaching hospitals	Emergency clinics
Population size	96	132†	168	139	606
Asymptomatic	86.3% (82/95)	25.0% (33/132)	60.1% (101/168)	75.5% (105/139)	88% (532/606)
No decontamination	12.2% (10/82)	–	29.7% (30/101)	–	3.8% (19/499)‡
Decontamination	87.8% (72/82)	–	69.3% (70/101)	–	96.2% (480/499)‡
Fluid therapy iv§	12.2% (10/82)	–	61.4% (62/101)		5.6% (15/269)
Symptomatic	14.7% (14/95)	43.2% (57/132)	40.5% (67/168)	24.5% (34/139)	12.2% (74/606)‡
Without AKI	13.7% (13/95)	10.6% (14/132)	29.8% (50/168)	18.7% (26/139)	12.0% (73/606)
With AKI	1.0% (1/95)	32.6% (43/132)	10% (17/168)	6.7% (8/120)¶	0.17% (1/606)
No decontamination	57% (8/14)	–	71.6% (48/67)	–	36.1% (26/72)‡
Decontamination	43% (6/14)	–	28.4% (19/67)	–	63.9% (46/72)‡
Fluid therapy iv§	35.7% (5/14)	–	74.6% (50/67)	–	19.4% (60/310)
Overall survival	100% (95/95)	–	92.3% (155/168)	92.3% (138/139)	100% (606/606)

PIC Poison information centre, DPIC Dutch Poisons Information Center, ASPCA American Society for the Prevention of Cruelty to Animals, VPIS Veterinary Poison Information Service, iv Intravenous, AKI Acute kidney injury

†A total of 132 medical records included, 41 dogs with poor historical information or poor prior health, 33 asymptomatic dogs, 14 symptomatic dogs without azotemia and 15 medical records involved co-ingestion confounding evaluation clinical course (Eubig *et al.* 2005)

‡A total of 571 dogs (499 asymptomatic and 72 symptomatic) information concerning decontamination and development clinical signs was completely available also for 579 dogs (269 asymptomatic and 310 symptomatic) information concerning intravenous fluid therapy and development clinical signs was completely available (Croft *et al.* 2021, suppl. 2)

§This includes iv fluid treatment *after* AKI had been diagnosed

¶A total of 120 animals with biochemical analysis

surveillance study, the overall incidence of clinical signs was 14.7% in dogs and 15.4% in cats. One dog and no cats were documented to develop AKI.

The incidence of *Vitis* fruit-induced AKI confirmed with serum biochemistry and urinalysis was only 1.0% in dogs and 0% in cats. The development of subclinical AKI cannot be excluded as serial biochemistry and urinalysis were often not performed. The incidence of clinical signs in dogs that, at least hypothetically, could be related to AKI (14.6%) as determined in the present study compares favourably with what has been described in previous retrospective studies with a range of 12.2 to 43.2% (Eubig *et al*. 2005, Sutton *et al*. 2009, Reich *et al*. 2020, Croft *et al*. 2021) (Table 5). However, a significant proportion of the clinical signs in dogs and all cats may be non-renal in origin. Anorexia, vomiting and diarrhoea developing within hours after ingestion are more likely due to local gastrointestinal distress caused by *Vitis* fruits, rather than by circulating uremic toxins (Mazzaferro *et al*. 2004). Furthermore, the incidence of proven *Vitis* fruit-induced AKI of 1% in our dogs was low illustrating that most clinical signs were unrelated to the development of AKI.

The presented patient sample demonstrates the difficulties in relating clinical signs at presentation to a *Vitis* fruit intake as many dogs suffer concurrent (chronic) medical conditions. In our population, three dogs were (chronically) treated with NSAIDs primarily because of arthrosis. They illustrate the necessity of biochemical analysis to confirm AKI and to consider other causes for the clinical signs, especially with medication that affects the gastrointestinal tract, like NSAIDs. On the other hand, in the dog with external otitis (Table 3, dog no. 12), the diagnosis of *Vitis* fruit-induced AKI was initially not considered as gastrointestinal signs in the first hours after *Vitis* fruit ingestion were absent. The worsening of the symptoms was ascribed to the treatment with gentamicin ointment, which is potentially nephrotoxic, and the anaesthesia applied to inspect the external ear canal for the already existing external otitis. Lack of gastrointestinal signs in the first hours after *Vitis* fruit ingestion has been noticed before by Reich *et al*. (2020). After close inspection of the time course, symptoms were noticed before gentamicin ointment was applied. And it was concluded that AKI was most likely induced by *Vitis* fruit ingestion, and it cannot be excluded that anaesthesia may have worsened the development of renal injury.

Over the years, a wide range of incidences of *Vitis* fruits-induced clinical signs (12.2 to 43.2%) and AKI (0.17 to 32.6%) have been reported (Table 5) (Eubig *et al*. 2005, Sutton *et al*. 2009, Reich *et al*. 2020, Croft *et al*. 2021). There are many factors making it difficult to compare the findings from these retrospective studies to our prospective study. Due to the retrospective nature of previous studies, the follow-up information on the clinical course of the patients included are often incomplete or lacking. The patient populations are often not comparable as the medical records that have been analysed were retrieved from data sources with different patient populations like a poison information centre (Eubig *et al*. 2005, Sutton *et al*. 2009), out-of-hours emergency clinics (Croft *et al*. 2021) and university teaching hospitals (Reich *et al*. 2020) and different in- and exclusion criteria have been used. Furthermore, the criteria for the diagnosis of AKI differ between studies; renal insufficiency has been defined based on the presence of oliguria, anuria, polydipsia, proteinuria, elevated serum concentrations of creatinine and urea (Sutton *et al*. 2009), or solely on (repeated) serum creatinine concentrations (Reich *et al*. 2020). Finally, it is sometimes unclear how the different subgroups add up to the total number of cases making it difficult to determine the incidence in the described population based on the published data (Eubig *et al*. 2005). When medical records are retrieved from similar data sources, *i.e*. poison information centre database, it is important to take into account the level of awareness of the general public and veterinarians of the potential danger of *Vitis* fruits. The medical records analysed by Sutton et al. are for example based on inquiries between 1994 and 2007, while the first report concerning *Vitis* fruit-induced AKI was published 2001. The DPIC registered between 2012 and 2020 a fivefold increase in *Vitis* fruits-related inquiries representing an increased awareness of both the general public and veterinarians. Over the years, the incidence of *Vitis* fruit-induced AKI in a poison information centre-related patient population decreased from 10% (32.6%) to 1% in this study and may decrease further when larger populations are analysed (Eubig *et al*. 2005, Sutton *et al*. 2009, Croft *et al*. 2021). To compile justifiable guidelines for the treatment of *Vitis* fruit ingestion for first-opinion practitioners, the patient sample should be similar to the population presented to these first-opinion practices. The aforementioned limitations in the retrospective studies question if the incidences currently determined in the literature, both for clinical signs and AKI, represent the incidences of a patient population presented to a first-opinion practice. The patient population in this study is more representable as a result of the prospective nature of the study and the collection of data that has been actively derived from veterinarians contacting the DPIC after being contacted directly by pet owners from the entire country during one full year. This study also differs from the previously mentioned retrospective studies as dogs on (chronic) NSAID treatment were included as they represent a significant group within the normal patient population. Based on the present study, the incidence of symptomatic *Vitis* fruit-induced AKI in dogs appears to be low (1.0%) in a patient population visiting a first-opinion veterinarian. This compares favourably with the results from the study by Croft that also represents a patient population from first-opinion (emergency) practices (Croft *et al*. 2021). However, these low incidences do not exclude the presence of subclinical kidney injury as creatinine and BUN have poor sensitivity to detect early decline in renal function. And although the DPIC protocol advised to monitor renal function for 3 days, serial measurements of creatinine were only sporadically performed, thereby likely missing subclinical AKI. Today more sensitive parameters like symmetric dimethylarginine (SDMA) and urinary neutrophil gelatinase-associated lipocalin are available, and it would be of scientific interest to use these more specific renal biomarkers in dogs ingestion *Vitis* fruits (Scheemaeker *et al*. 2020, Sargent *et al*. 2021).

It is likely that cats are not very susceptible for *Vitis* fruits-induced AKI based on our data and the literature search, with only one publication reporting two cats with AKI after the ingestion of *Vitis* fruits with no further details on the circumstances (Sutton *et al*. 2009).

All previous studies including the present one are observational therefore the treatment instituted by the veterinarians is not uniform. In this prospective follow-up study, the suggested treatment guidelines for *Vitis* fruits ingestion were in most cases not or just partially applied (Table 5). Compliance to the suggested treatment guidelines, especially in asymptomatic animals is determined by many factors; the incidence of developing severe signs of poisoning, the personal experience of the first-opinion veterinarian and the financial burden to owner (Williams *et al*. 2020). In the Netherlands, approximately 4% of the owners have a pet health insurance; therefore, primary case is often limited to decontamination measures and baseline and serial renal values and urinalysis are often refused by the owner (Van Heijst *et al*. 2015).

Comparable with previous studies, decontamination measures were more often instituted in dogs that eventually remained asymptomatic compared to symptomatic dogs. The percentage decontaminated, symptomatic dogs between the different studies varies between 28.4 and 63.9% (Table 5). But, with more symptomatic dogs decontaminated, the incidence of symptomatic dogs developing *Vitis* fruits-induced AKI appears to decrease. Whether decontamination measures are instituted is predominantly determined by the time frame between ingestion and presentation at a veterinary clinic (in general within 2 to 4 hours postingestion) and whether it can be performed safely (Kan *et al*. 2016). In most dogs, vomiting was induced and emesis was successful in removing grapes from the stomach even after 12 hours postingestion. In our study in eight symptomatic dogs, including the dog developing AKI, no decontamination was applied and many of these dogs were presented too late to make decontamination measures effective (Table 3).

Intravenous fluid therapy for at least 48 hours to prevent hypovolaemia/dehydration and enhance diuresis was applied in only four dogs and one cat. None of these animals developed signs of AKI. The contribution of intravenous fluid therapy in preventing the development of *Vitis* fruits-induced AKI cannot be evaluated as with the low incidence, it is not possible to determine if this potentially preventive measure could be effective. Furthermore, in many studies, it is often unclear whether intravenous fluid therapy is instituted to prevent or treat AKI. Therefore, no conclusions can be drawn from the effect of fluid therapy in preventing *Vitis* fruits-induced renal injury. On the other hand, the *Vitis* fruit-induced AKI incidence is low while only a few animals received intravenous fluid therapy.

In conclusion, a significant proportion of the dogs and cats (~15%) will develop signs and symptoms after ingestion of *Vitis* fruits, which are predominantly related to gastrointestinal distress. However, a very limited number of dogs develop symptomatic AKI, particularly if proper decontamination measures are applied. Emesis is very successful in removing grapes from the stomach and can be effective many hours postingestion. Whether it is necessary to administer activated charcoal after successful vomiting remains uncertain as the toxin responsible for AKI has not yet been fully elucidated. It is, therefore, unknown if it will bind to activated charcoal. Fluid therapy should be instituted to treat or prevent hypovolaemia/dehydration as a result of a-/hypodipsia, vomiting and diarrhoea. The contribution of intravenous fluid therapy in asymptomatic animals for a minimum of 48 hours for preventing AKI development needs further investigation. Baseline evaluation of renal function, specific gravity of the urine and/or urinalysis is recommended. In all dogs that develop clinical signs ≥24 hours postingestion, evaluation of renal function is recommended followed by renal support measures if indicated. In cats, induction of emesis can be considered, but is not sufficiently supported by current publications. Fluid balance needs to be maintained under all circumstances, but fluid therapy in order to prevent AKI development may be unnecessary based on the current, limited scientific information available.

Conflict of interest

None of the authors of this article has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

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