Revista de Medicina Veterinaria

Volume 1 | Number 42 Article 11

2021-05-12

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Citación recomendada

Gülersoy E, Kaan Durgut M, Serhat İyigün S y Sevinç M. Syrup Hedera helix Extract Poisoning in Dog: a Clinical Report. Rev Med Vet. 2021;(42):. doi: https://doi.org/10.19052/mv.vol1.iss42.11

Rev. Med. Vet. Bogotá (Colombia) N.° 42, enero-junio del 2021
ISSN: 0122-9354 - ISSN-e: 2389-8526 (en línea)
Online First

Revista de Medicina Veterinaria

https://doi.org/10.19052/mv.vol1.iss42.11

Syrup *Hedera helix* Extract Poisoning in Dog: a Clinical Report[1]

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Recibido: 27 de septiembre de 2020**. Aceptado:** 17 de octubre de 2020. **Online First:**5 de mayo de 2021

Cómo citar este artículo: Gülersoy E, Kaan Durgut M, Serhat İyigün S, Sevinç M. Syrup hedera helix extract poisoning in dog: a clinical report. Rev Med Vet. 2021;(42). https://doi.org/10.19052/mv.vol1.iss42.11

Abstract

This clinical report describes a 1-year-old Golden Retriever dog weighing 24 kg that developed gastroenteritis as a result of the unprescribed and random use of a syrup *Hedera helix* extract, which is for human use only. Diagnosis was made after ruling out other factors that could cause gastroenteritis. An improvement in clinical findings was observed as a result of supportive treatment. It is already widely recognized that triterpene saponins, biological active compounds of *Hedera helix*, cause gastroenteritis in dogs and it is considered that unprescribed and random use of syrup *Hedera helix* at high doses, may cause severe gastroenteritis symptoms that will endanger life. It is concluded that successful management of *Hedera helix* extract poisoning depends on a good anamnesis, physical exams, and laboratory tests, rapidly ruling out other causes of gastroenteritis, quitting the use of syrup immediately and a supportive treatment.

Keywords: *Hedera helix*, gastroenteritis, dog, unprescribed medicine.

[1] Study case

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Resumen

En este informe clínico se describe un cuadro de gastroenteritis desarrollada por un golden retriever de 1 año que pesaba 24 kg, como resultado del uso aleatorio y sin receta de un extracto de jarabe de *Hedera helix*, que es solo para uso por humano. El diagnóstico se realizó después de que se descartaron otros factores que podrían causar gastroenteritis. Se observó una mejora en los hallazgos clínicos como resultado del tratamiento de apoyo. Ya se ha reconocido ampliamente que las saponinas triterpénicas, que son compuestos biológicos activos de *Hedera helix*, causan gastroenteritis en perros, y se considera que el uso aleatorio y sin receta de jarabe de extracto de *Hedera helix* en dosis altas puede provocar síntomas de gastroenteritis más graves que pondrán en peligro la vida. Se concluyó que el manejo exitoso de la intoxicación por *Hedera helix* depende de una buena anamnesis, exámenes físicos y de laboratorio, descartar rápidamente las otras causas de gastroenteritis, dejar inmediatamente el jarabe y tratamiento de apoyo.

Palabras clave: *Hedera helix*, gastroenteritis, perro, medicamento sin receta.

INTRODUCTION

Hedera helix (ivy leaf), one of the 15 species of the genus Hederae, is an evergreen ivy from the Araliaceae family. Ivys are found naturally in Asia, North America, Eastern, Central and Southern Europe. It is a common decorative plant. The biological active compund responsible for the medical use of *Hedera helix* are triterpene saponins. The saponins are naturally occurring surface-active glycosides. They are mainly produced by plants such as soyabean, yucca and English ivy but also by lower marine animals such as sea cucumber and starfish (1,2). Of these saponins, 1.7-4.8 % is hederacoside C, 0.4-0.8 % is hederacoside D, 0.1-0.2 % is hederacoside B and 0.1-0.3 % is α-hederin. As a result of preclinical studies, it has been shown that ivy leaf extracts have bronchodilator, spasmolytic and antibacterial effects, especially α-hederin with secretolytic and bronchospasmolytic properties (3).

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The fresh fruits and leaves of *Hedera helix* ivy are toxic and can cause gastrointestinal tract mucosa irritation, bloody diarrhea and even death (4). The well-known side effect is contact dermatitis and many cases have been reported (5-7). Hausen et al. (8) reported that ivy leaf is a strong irritant based on chemical, laboratory and clinical studies. Therefore, *Hedera helix,* which contains 10 % α and ß hederin saponins, is very irritant to mucosal surfaces (9).

Apart from the improper use of drugs resulting from therapeutic errors, drug intoxications in adult humans are often caused by misuse, abuse or conscious suicide. In children and animals, the cause of poisoning with over-the-counter drugs is often accidental ingestion and exposure to the drugs when they are not under supervision by a caretaker. Albeit many over-the-counter drugs are not highly toxic; affected animal's age and size, the amount of the drug ingested, and the duration of the exposure play a role in severity of the poisoning symptoms (10).

Most commonly reported unprescribed medication toxicities are nonsteroidal anti-inflammatory drug poisoning such as aspirin poisoning, causing gastric irritation because of enterohepatic recycling in cats and dogs; ibuprofen poisoning, causing nausea, vomiting, abdominal pain, gastrointestinal ulceration and mild central nervous system depression; naproxen poisoning; causing gastrointestinal signs along with renal insufficiency; acetaminophen poisoning, causing liver necrosis; and common flu drugs such as antitussives and antihistamines, causing gastrointestinal lesions with mydriasis, dry mucous membranes, disorientation and may show fever in cats and dogs (10,11). Therefore, the potential for deliberate abuse of these drugs always exists and should always be considered when such poisoning is suspected. For this reason, this report aims to describe the clinical consequences of unprescribed use of *Hedera helix* extract as well as the case management.

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CASE PRESENTATION

A 1-year-old, vaccinated, not neutered male Golden Retriever dog, weighing 24 kg, admitted to the Selcuk University Veterinary Faculty Animal Hospital with complaints of vomiting, diarrhea, anorexia and excessive salivation. In the anamnesis, it was learned that the dog lived at home, had not recently changed its diet and was fed commercial food, and was taken out for a walk twice a day. It was admitted to a veterinary clinic with a complaint of cough 2 months before the admission to our hospital, where it was diagnosed with tracheitis, and antibiotics (Ceftriaxone) and antitussives (Butamirate citrate) were prescribed. However, it was learned that the owner of the patient did not administer the prescribed drugs and gave Prospan® (Engelhard Arzneimittel GmbH & Co. KG, Germany) syrup to the dog 3 times a day for 30 days (total daily dose 105 mg).

In the clinical examination, abdominal pain, severe salivation and dehydration were detected along with normothermia. Following physical examination, blood samples were taken from the cephalic vein by venous puncture for blood gas test, complete blood count (CBC) and serum biochemistry. Fecal examination was performed to rule out the parasitic factors that could cause gastrointestinal symptoms such as vomiting, diarrhea and nausea. Canine Parvovirus (CPV), Canine Coronavirus (CCV) and Canine Distemper Virus (CDV) rapid tests (ASAN Pharm Easy Test®, Korea) were performed. Rapid test results were negative. No parasites were detected on fecal examination. Radiographic and ultrasonographic examinations were performed to rule out any suspicion of foreign body or invagination. No abnormal finding was observed. In the laboratory studies, mild metabolic acidosis and base deficit in blood gases and azotemia, a significant increase in AST, ALP, LDH and CPK enzyme levels in serum biochemistry were detected. CBC findings were within the normal reference range (Table 1).

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Table 1. Blood gases, CBC and serum biochemistry findings

Parameter	Value	Reference	Parameter	Value	Reference
pH	**7.31**	7.35-7.45	**BUN**	**12.7 mg/dl**	5.6-11.8
K	4.3 mmol/L	3.4-5.6	**Creatinine**	**1.6 mg/dl**	0.5-1.5
Na	**148 mmol/L**	150-165	**AST**	**229 U/L**	10-88
Cl	121 mmol/L	104-128	**ALT**	**90 U/L**	10-88
Lactate	**4.7 mmol/L**	0-2	**ALP**	**169 U/L**	20-150
Glucose	92 mg/dl	80-120	Glucose	110 mg/dl	60-110
Base excess	**-10.4 mmol/L**	-4- 4	Amylase	1707 U/L	300-2000
HCO_3	**16.1 mmol/L**	19-24	**LDH**	**898 U/L**	50-495
WBC	9.63 m/mm^3	6-17	T. bil	0.2 mg/dl	0.1-0.6
Lymphocyte	2.33 m/mm^3	0.6-5.1	D. bil	0.1 mg/dl	0-0.3
Monocyte	1.41 m/mm^3	0.1-1.7	Phosphorus	3.3 mg/dl	2.2-5.5
Granulocyte	5.89 m/mm^3	3-13.6	Cholesterol	168 mg/dl	125-270
RBC	6.04 M/mm^3	5.5-8.5	Albumin	2.7 g/dl	2.3-3.8
MCV	73.2 fl	58-73	Calcium	8.6 mg/dl	8.6-11.2

MCH	24.1 pg	19.5-24.5	Triglyceride	57 mg/dl	20-112
Hb	14.6 g/dl	15.5	**CPK**	**277 U/L**	20-200

K: Potassium, Na:Sodium, Cl: Chlorine, HCO_3: Bicarbonate, WBC: White blood cells, RBC: Red blood cells, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, Hb: Hemoglobin, BUN: Blood urea nitrogen, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, ALP: Alkaline phosphatase, LDH: Lactate dehydrogenase, T.Bil: Total bilirubin, D. Bil: Direct bilirubin, CPK: Creatin phosphokinase

Source: own work

For a symptomatic treatment, fluid therapy (0.9 % Isotonic solution, Polifleks, Polifarma®, 60 ml/kg IV, SID), antiemetic (Maropitant, Cerenia, Pfizer®, 1 mg/kg SC, SID), gastric protectant (Ranitidine, Ranixel, Menta Pharma®, 2mg/kg IV, BID), vitamin and mineral supplements (Duphalyte, Zoetis®, 10 ml/kg IV, SID) were administered intravenously for 3 days. Prospan® syrup was discontinued. Appetite was restored 3 days after the treatment and it was observed that all clinical symptoms resolved.

Based on clinical examination and laboratory tests, factors that could cause gastrointestinal disease symptoms such as kidney disease, liver disease, diabetic ketoacidosis, pancreatitis, parasitic, viral and bacterial factors, foreign bodies, and diet change were ruled out, and the cause of gastroenteritis was evaluated as *Hedera helix* extract poisoning.

DISCUSSION AND CONCLUSION

In the last few decades, there has been a rapid increase in the field of herbal medicine in both developed and developing countries due to its natural origin and fewer side effects. Metabolites used in many fields such as pharmacology, agrochemistry, color and food additives are obtained from plants. *Hedera helix* also contains a wide variety of metabolites and pharmacological agents. Its traditional use is the symptomatic

treatment of cough in common flu and acute or chronic inflammatory bronchial diseases in humans. In addition, it has expectorant, analgesic, and anti-inflammatory effects. Preliminary studies on the phytochemical analysis of *Hedera helix* revealed that the plant contains unsaturated sterols, tannins, phenolic components, glycosides, alkaloids, carbohydrates, sugars and saponins. The concentration of 25-320 μM of α-hederin, one of these saponins, significantly changes the spontaneous motor activity of the smooth muscle in the rat stomach (12). Likewise, it was reported that daily oral use of 1.5 gr/kg dry ivy leaf for 100 days did not have hematological, biochemical, and histological effects in rats, but 4 gr/kg for 90 days of use had hemolytic effects (13).

Some investigators reported (2,14,15,16) that as dietary saponins are poorly absorbed, their biological effects occur in the gastrointestinal tract. Some saponins increase intestinal mucosal cell permeability in vitro, inhibit active mucosal transport and facilitate uptake of waste substances. An increase in the permeability of the brush border observed at sublethal levels of saponins may have important implications for the uptake of macromolecules, such as allergens, resulting in gastrointestinal signs such as vomiting and diarrhea.

There are several reported negative effects of saponins in single-stomached animals such as reduced feed intake caused by the irritating properties of saponins (17), reduction in the intestinal motility, reduction in protein digestibility (18) and damage to the intestinal membrane and inhibition of nutrient transport through intestinal tract (2). Lanza et al. (19) reported that oral use of ivy leaf dry extract (containing 66 % ethanol) in rats at a dose of 3-4.1 g/kg did not cause death in the first 72 hours, but caused diarrhea. On the other hand, oral use at a dose of 2.8-4.7 g/kg has been reported to cause death within the first 48 hours, and diarrhea was the only observed symptom before death. It is reported that dry extract of ivy leaf at an oral dose of 1.5 gr/kg daily for 100 days does not show toxic effects in rats. In the study, no abnormality

was observed in any hematological and biochemical parameters and histopathological findings of the kidney and liver compared to the control group. Haemolytic effect has been reported in oral use of 4 gr/kg daily for 90 days as mentioned above.

In a study researching the toxicity and absorption kinetics of the triterpene saponins in mice and dogs, it was observed that the non-toxic intravenous dose for oleane triterpene saponin was 0.01 mg/kg and only minor effects were noted at 0.1 mg/kg. The liver is the primary target for toxicity with lesions such as focal hepatocellular necrosis. This is also reflected in the blood as a mild to moderate increase of the liver enzymes within 24 hours (20). In the same study it was also determined that increase in the liver enzymes such as ALT, AST, ALP and pathological changes such as hepatocellular necrosis and vacuolization were the most significant toxic signs. The increase in AST ALT and ALP liver enzymes in our case can be attributed to liver parenchymal damage caused by syrup *Hedera helix*.

In this clinical report, gastroenteritis was attributed to the random and unprescribed administration by the owner of Prospan® syrup, which contains 0.7 g dry ivy helix folium extract in 30 % ethanol solvent. In this case, it was observed that daily oral use of Prospan® for 30 days at a dose of 4.3 mg/kg caused gastroenteritis in the dog, and that supportive treatment consisting of fluid therapy, antiemetic, gastric protectants and vitamin mineral supplements was sufficient to relieve clinical symptoms. The limitations of this case report are the fact that serum concentrations of triterpene saponins, the bioactive substance of *Hedera helix*, could not be determined and that the gastrointestinal mucosa and liver damage was not histopathologically evaluated. It was concluded that the successful management of *Hedera helix* extract poisoning depends on a differential diagnosis as gastroenteritis is a broad term and has many potential causes —being *Hedera helix* extract poisoning one of them— and requires quitting the use of syrup immediately and a supportive

treatment. In addition, it is advisable to educate the public about the potential risks of over-the-counter drugs as it is usual for pet owners to give their pets the medicines they use for themselves.

REFERENCES

1. Hostettmann K, Marston A. Saponins. Cambridge: Cambridge University Press; 1995. https://doi.org/10.1017/CBO9780511565113
2. Das TK, Banerjee D, Chakraborty D, Pakhira MC, Shrivastava B, Kuhad RC. Saponins: Role in Animal System. Vet World. 2012;5(4):248-54. https://doi.org/10.5455/vetworld.2012.248-254
3. Lutsenko Y, Bylka W, Matlawska I, Darmohray R. *Hedera helix* as a medicinal plant. Herba Polonica 2010; 56(1):84-96.
4. Baytop T (1984) Therapy with medicinal plants in Turkey (Past and present). Istanbul: Publications of the Istanbul University; 1984. p. 225.
5. Garcia M, Fernandez E, Navarro JA, del Pozo MD, Fernandez de Correz L. Allergic contact dermatitis from *Hedera helix* L. Contact Dermatitis. 1995;33(2):133-4. https://doi.org/10.1111/j.1600-0536.1995.tb00523.x.
6. Massmanian A, Valcuende-Cavero F, Ramirez-Bosca A, Castells-Rodellas A (1988) Contact dermatitis from variegated ivy (*Hedera helix* subsp. *canariensis* Willd.). Contact Dermatitis. 1988;18(4): 247-8. https://doi.org/10.1111/j.1600-0536.1988.tb02818.x
7. Süleyman H, Mshvildadze V, Gepdiremen A, Elias R. Acute and chronic anti-inflammatory profile of the ivy plant, Hedera helix, in rats. Phytomedicine. 2003; 10(5): 370-4. https://doi.org/10.1078/0944-7113-00260

8. Hausen BM, Brohan J, Konig W A, Faasch H, Hahn H, Bruhn G. Allergic and irritant contact dermatitis from falcarinol and didehydrofalcarinol in common ivy (*Hedera helix* L.). Contact Dermatitis. 1987;17(1):1-9. https://doi.org/10.1111/j.1600-0536.1987.tb02634.x

9. Paulsen E, Christensen LP, Andersen KE. Dermatitis from common ivy (*Hedera helix* L. subsp. *Helix*) in Europe: past, present and future. Contact Dermatitis. 2010;62(2): 201-9. https://doi.org/10.1111/j.1600-0536.2009.01677.x

10. Fitzgerald KT, Bronstein AC, Flood AA. "Over-The-Counter" Drug Toxicities in Companion Animals. Clin Tech Small Anim Pract. 2006; 21(4): 215-26. https://doi.org/10.1053/j.ctsap.2006.10.006

11. Talcott PA. Nonsteroidal anti-inflammatories. In Peterson ME, Talcott PA (eds): Small Animal Toxicology. St. Louis, MO. Elsevier; 2006. pp. 902-33. https://doi.org/10.1016/B0-72-160639-3/50067-8

12. Mendel M, Chłopecka M, Dziekan N and Wiechetek M. The effect of the whole extract of common ivy (*Hedera helix*) leaves and selected active substances on the motoric activity of rat isolated stomach strips. J Ethnopharmacol. 2011;134(3):796-802. https://doi.org/10.1016/j.jep.2011.01.036

13. Al-Snafi AE. Pharmacological and therapeutic activities of Hedera helix-a review. IOSR Journal of Pharmacy 2018;5(1):41-53.

14. Johnson IT, Gee JM, Price K, Curl C, Fenwick GR. Influence of saponins on gut permeability and active nutrient transport in vitro. J Nutri 1986; 116(11): 2270-77. https://doi.org/10.1093/jn/116.11.2270

15. Cheeke, PR. Biological effects of feed and forage saponins and their impact on animal production. In GR Waller and Y Yamasaki, editors, Saponins Used in Food and Agriculture. New York: Plenum Press; 1996. pp. 377-86. https://doi.org/10.1007/978-1-4613-0413-5_32

16. Gee JM, Wortley GM, Johnson IT, Price KR, Rutten AAJJL, Houben GF and Penninks AH. Effect of saponins and glycoalkaloids on the permeability and viability of mammalian intestinal cells and on the integrity of tissue preparations in vitro. Toxicol. 1996;10(2):117-28. https://doi.org/10.1016/0887-2333(95)00113-1

17. Oleszek W, Nowacka J, Gee JM, Wortley G and Johnson IT. Effects of some purified alfalfa (*Medic ago sativa*) saponins on transmural potential difference in mammalian small intestine. J Sci Food Agri 1994;65(1):35-9. https://doi.org/10.1002/jsfa.2740650107

18. Shimoyamada M, Ikedo S, Ootsubo R and Watanabe K. Effects of soybean saponins on chymotryptic hydrolyses of soybean proteins. J Agric Food Chem. 1998;46(12):4793-7. https://doi.org/10.1021/jf980694j

19. Lanza JP, Steinmetz MD, Pellegrin E, Mourgue M. Actions toxique et pharmacodynamique sur le rat d'extraits de lierre grimpant (*Hedera helix* L.). Plant Med Phytothér. 1980;14(4):221-9.

20. Maes L. Intravenous and subcutaneous toxicity and absorption kinetics in mice and dogs of the antileishmanial triterpene saponin PX-6518. Molecules. 2013; 18(4):4803-15. https://doi.org/10.3390/molecules18044803