P-ISSN: 2304-3075; E-ISSN: 2305-4360
International Journal of Veterinary Science
www.ijvets.com; editor@ijvets.com

Case Report https://doi.org/10.47278/journal.ijvs/2023.028

Thrombocytopenia in a Dog Due to Long-Term Administration of Phenylpropanolamine: A Case Report

Romana Bielik[1], Peter Korim[1], Imrich Kašelák[1], Branislav Lukáč[2] and Bohumil Bielik[2]*

[1]Department of Public Veterinary Medicine and Animal Welfare, University of Veterinary Medicine and Pharmacy, Komenského 73, 041 81 Košice, Slovak Republic.
[2]Small Animal Clinic, University of Veterinary Medicine and Pharmacy, Komenského 73, 041 81 Košice, Slovak Republic.
***Corresponding author:** bohumil.bielik@uvlf.sk

Article History: 23-127 Received: 26-Jan-23 Revised: 07-Feb-23 Accepted: 14-Feb-23

ABSTRACT

This report describes a clinical case with presentation of thrombocytopenia in a 14-year-old American Cocker Spaniel due to long-term oral administration of phenylpropanolamine and its successful management. This is the first case report of a dog with thrombocytopenia associated with the use of phenylpropanolamine.

Key words: Phenylpropanolamine, Coagulopathy, Thrombocytopenia

INTRODUCTION

Phenylpropanolamine (PPA) is a sympathomimetic amine structurally similar to amphetamines (Cantu et al. 2003) and an α-agonist most frequently used to treat urinary incontinence in spayed dogs by increasing urethral sphincter tone (Byron et al. 2007). Side effects of amphetamines include severe hyperthermia, coagulopathy, and petechial bleeding (Brust 2016). In veterinary medicine, side effects after administration of PPA in dogs, particularly systemic hypertension, have been reported at increasing rates. One of such case reports describes hypertensive retinopathy with hyphemia and retinal detachment in a 4-year-old Labrador retriever (Crandell et al. 2005). Segev et al. (2015) proved a significant increase in systolic, diastolic, and mean blood pressure 12h after PPA administration in a group of dogs treated with PPA when compared with a control group. In addition, Peterson et al. (2011) presented a retrospective case study with a wide variety of clinical signs in dogs, including agitation, vomiting, mydriasis, tremor, bradycardia, tachycardia, and hypertension. In human medicine, common but serious side effects of PPA include hypertension, headache, seizures, and hemorrhages. As a consequence, the FDA banned products containing PPA in November 2000. This was underlined by a 5-year case-control study published by the Hemorrhagic Stroke Project (Aronson 2016), which involved 702 patients with hemorrhagic strokes. As far as the authors are aware, thrombocytopenia has not been reported yet as a potential side effect of PPA in veterinary medicine. The purpose of this report is to describe a rare side effect of PPA in a dog.

CASE PRESENTATION

History

A 14-year-old intact male American Cocker Spaniel dog (11.2kg) was presented as an emergency case at the Small Animal Clinic, the University of Veterinary Medicine and Pharmacy, Košice, with a two-day history of lasting apathy, anorexia, melena, and hematemesis. The patient had been treated solely with antiemetics (Metoclopramide 0.5mg/kg s.c.) at another veterinary clinic, no other examinations or treatment had been performed at the clinic. During the initial visit, owners stated that the dog had not had any problems prior to his current illness and had not received any drugs recently. The dog was fully vaccinated and treated against parasites (Simparica, Zoetis, Louvain-la-Neuve, Belgium).

Clinical Examination

Physical examination results: rectal temperature 39.17°C, tachypnoea (42breaths/min), tachycardia (approximately 185beats/min), blood pressure measured on the tail - 184/78mmHg. The dog had anemic mucosal membranes with petechiae. Petechiae and ecchymoses were also found on the skin of the caudal abdomen and inguinal regions.

Cite This Article as: Bielik R, Korim P, Kašelák I, Lukáč B and Bielik B, 2023. Thrombocytopenia in a dog due to long-term administration of phenylpropanolamine: A case report. International Journal of Veterinary Science 12(6): 897-899. https://doi.org/10.47278/journal.ijvs/2023.028

Hematology (Procyte Dx Hematology Analyzer, IDEXX Laboratories, Inc, Westbrook, ME, USA) revealed normocytic hypochromic non-regenerative anemia RBC 4.16T/L (reference interval (RI): 5.65-8.87), PCV 24.3% (RI: 37.3–61.7%); leukocytosis 27.79x10^9/L (RI): 5.05–16.76x10^9/L); neutrophilia 22.38x10^9/L (RI: 2.95 to 11.64x10^9/L); and monocytosis 3.33x10^9/L (RI: 0.16-1.12x10^9/L). Biochemistry (Cobas C111 Analyzer, Roche Diagnostics GmbH, Mannheim, Switzerland) revealed increased alanine aminotransferase (ALT) 2.95µkat/L (RI to 0.949µkat/L), ALP 5.72µkat/L (RI to 1.24µkat/L), LPS 4.5µkat/L (RI to 1.66µkat/L), UREA 18.93 mmol/L (3.97to 8.05mmol/L), BIL T 4.1µmol/L (to 3.1µmol/L), no other abnormalities were noted within RI. Platelets were 0K/µL (RI 148-484 K/µL) and Citrated PT has shown 7seconds, i.e. within the reference range 11–17s. APTT was within the reference interval. Buccal membrane bleeding time exceeded 5.5min. A blood smear was performed with no spherocytes, erythrocytes were normal sized, without *Babesia spp.* presented in erythrocytes, platelet aggregation in blood smear was found with a low count of free platelets. Snap 4Dx plus (IDEXX Laboratories, Inc, Westbrook, ME, USA) was negative for *Anaplasma phagocytophilum, A. platys, Borrelia burgdorferi, Ehrlichia canis, E. ewingii, and Dirofilaria immitis*. Thoracic and abdominal radiographs were unremarkable. Ultrasound findings were unremarkable.

Table 1: Hematobiochemical values of the dog at initial examination

Parameters	Units	Findings	Reference Interval
PCV/Hematocrit	%	24.3	37.3-61.7
RBC	T/L	4.16	5.65-8.87
WBC	x10^9/L	27.79	5.05-16.76
Neutrophils	x10^9/L	22.38	2.95-11.64
Monocytes	x10^9/L	3.33	0.16-1.12
ALT	µkat/L	2.95	up to 0.949
ALP	µkat/L	5.72	up to 1.24
LPS	µkat/L	4.5	up to 1.66
UREA	mmol/L	18.93	3.97-8.05
BIL T	µmol/L	4.1	up to 3.1
PLT	K/µL	0	148-484

Treatment

Based on the clinical findings, metronidazole (Efloran, KRKA, Novo Mesto, Slovenia) 15mg/kg body weight (BW), IV, q12h, acidum methylphenoxypropionicum (Hepagen, BIOPHARM, Chotoun, Czech Republic) 1mL/kg BW, IV, q24h, maropitant (Cerenia, Zoetis, New Jersey, USA) 1mg/kg BW, IV, q24h, famotidine (Quamatel, Gedeon Richter Plc., Budapest, Hungary) 1mg/kg BW, IV, q12h, metamizole (Novalgin, Sanofi - Aventis, Bratislava, Slovak Republic) 25mg/kg BW, IV, q12h, nadroparin 2850IU (anti-Xa) / 0.3mL SC q24h (Fraxiparine Glaxo Wellcome Production, Évreux, France), balanced crystalloid solution (Gelofusine B. Braun, Melsungen, Germany) 2mL/kg BW per hour IV were administered.

During the night, the patient had bloody diarrhea but without emesis. On day 2, the owners admitted that they had been administering phenylpropanolamine (Propalin Sirup Vétoquinol, Lure, France) 1.5mg/kg BW, PO, q12h for approximately two years and in addition, they had observed bleeding gums a few times per month for more than half a year.

On day 3, the dog was in a good clinical condition without fever, diarrhea, or emesis. He was eating normally. No petechiae or purpura were found in the oral cavity. Hematology results showed decreasing PCV of 23.6%, no reticulocytosis, leukocytosis 49.46x10^9/L, neutrophilia 33.67x10^9/L, lymphocytosis 9.29x10^9/L (RI: to 5.10x10^9/L), and monocytosis 6.38x10^9/L, platelets 58K/µL without aggregation in a blood smear. Zone electrophoresis on agarose gel was performed to describe the electrophoretic pattern of serum protein and distribution of protein fractions, with no remarkable changes in β and γ-globulin fractions found. Based on the hematology test results, ceftriaxone (Ceftriaxon, Sandos GmbH, Holzkirchen, Germany) 30mg/kg BW, IV, q12h, was added.

A hematology test performed on day 5 showed reticulosis 254K/µL (RI 10–110K/µL) with platelets in RI. The dog continued receiving ceftriaxone and nadroparin. The blood pressure measured on the tail was 162/70mmHg.

On day 7, hematology test results showed improvement of PCV 29.5% with reticulocytosis 660K/µL and decreasing WBC 29.64x10^9/L, neutrophils 19.97x10^9/L, lymphocytes 7.45x10^9/L and monocytes 2.04x10^9/L. Platelets were in RI and PT time was 9.6s. The dog was sent home with nadroparin to be administered for next four days.

On day 11, the dog returned for a follow-up. While at home, the dog´s appetite had been good, without problems. Hematology test results revealed reticulocytosis 163.9K/µL with correction of anemia PCV 36.6%; WBC, NEU LYM, platelets PT, and APTT were within RI. The dog came for a follow-up a month later and at that time, all his hematology parameters were within the reference interval and blood pressure was 148/62mmHg.

DISCUSSION

Thrombocytopenia is a common finding in critically ill veterinary patients, regardless of the diagnosis at admission (Gkaliagkousi et al. 2010; Yang and Bi 2022). There are three main causes of thrombocytopenia: 1) decreased platelet production in the bone marrow, 2) increased platelet destruction, and 3) abnormal sequestration.

In this case, we present thrombocytopenia mediated by the prolonged administration of PPA, which had lasted for over two years. This patient´s thrombocytopenia could be a very rare side effect of the drug caused by two different mechanisms, one of them being hypertension - a very common side effect of PPA usage in dogs (Peterson et al. 2011; Segev et al. 2015) and even in humans (Glass 1989; Cantu 2005). Platelet aggregation caused by hypertension is well known in human medical practice, although no research suggests a direct link between hypertension and platelet aggregation/activation (Davis et al. 2021). Potential mechanisms also include endothelial dysfunction and platelet degranulation (Gkaliagkousi et al. 2010). Drug-induced thrombocytopenia (DIT) could be the other mechanism behind the development of thrombocytopenia in the presented dog. Administration of

certain drugs causes DIT either by suppressing megakaryocytes in the bone marrow or by generalized marrow stem cell suppression, which is accompanied by increased platelet destruction and consumption. Platelets usually return to normal after the drug is discontinued (MSD). Thrombocytopenia and thrombocytopenic purpura are very rarely reported symptoms (less than 0.01%) of amphetamines usage in humans. Glass et al. (1989) reported on a human patient with thrombocytopenia after administration of diet pills containing PPA.

In conclusion, this is the first report of a dog with thrombocytopenia associated with long-term administration of phenylpropanolamine.

Funding Statement

This work was supported by the Ministry of Education, Science, Research and Sport of the Slovak Republic (Grants No. CEGA No. 008UVLF-4/2020).

Author's Contribution

All authors contributed equally to this work.

REFERENCES

Aronson JK 2016. Chapter. Phenylpropanolamine (norephedrine). In Meyler´s Side Effects of Drugs. Elsevier. Amsterdam Netherland, pp: 705-708.

Brust JCM 2016. Chapter 39 – Stroke and Substance Abuse. In Stroke, Elsevier. Amsterdam Netherland, pp: 648-657.

Byron JK, March PA, Chew DJ and DiBartola SP, 2007. Effect of phenylopropanolamine and pseudoephedrine on the urethral pressure profile and continence scores of incontinent female dogs. Journal of Veterinary Internal Medicine 21: 47-53. https://doi.org/10.1892/0891-6640(2007)21[47:eopapo]2.0.co;2

Cantu C, Arauz A, Murillo-Bonilla LM, López M and Barinagarrementeria F, 2003. Stroke associated with sympathomimetics contained in over-the-counter cough and cold drugs. Stroke 34**:** 1667–1673. https://doi.org/10.1161/01.STR.0000075293.45936.FA

Crandell JM and Ware WA, 2005: Cardiac toxicity from phenylpropanolamine overdose in a dog. Journal of The American Animal Hospital Association 41**:** 413–420. https://doi.org/10.5326/0410413

Davis M, Movahed MR, Hashemzadeh M and Hashemzadeh M, 2021: Evaluating association between idiopathic thrombocytopenic purpura and hypertension. American Journal of Blood Research 11: 405-409.

Gkaliagkousi E, Passacquale G, Douma S, Zamboulis C and Ferro A, 2010: Platelet activation in essential hypertension: implications for antiplatelet treatment. American Journal of Hypertension 23: 229-236. https://doi.org/10.1038/ajh.2009.247

Glass JT, Williams JP and Mankad VN, 1989. Intracranial hemorrhage associated with quinidine induced thrombocytopenia. Journal of the Medical Association of the State of Alabama 59: 24–25.

Peterson KL, Lee JA and Hovda LR. 2011: Phenylpropanolamine toxicosis in dogs: 170 cases (2004-2009). Journal of The American Animal Hospital Association 239: 1463-1469. https://doi.org/10.2460/javma.239.11.1463

Segev G, Westropp JL, Kulik C and Lavi E, 2015. Changes in blood pressure following escalating doses of phenylpropanolamine and a suggested protocol for monitoring. Canadian Veterinary Journal 56: 39–43.

Yang X and Bi F, 2022. Diagnosis and treatment of feline immune-mediated thrombocytopenia. Agrobiological Records 9: 58-61. https://doi.org/10.47278/journal.abr/2022.016