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CASE REPORT

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Successful treatment of a severe cannabinoid toxicity using extracorporeal therapy in a dog

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Abstract

Objective: To describe the use of extracorporeal therapy (ECT) to treat severe cannabinoid intoxication in a dog with severe hyperlipidemia.

Case Summary: A 7-month-old female intact Labrador Retriever presented with seizures and severe hyperesthesia that were refractory to multiple anticonvulsant medications and required induction of general anesthesia with propofol and mechanical ventilation. The dog's urine yielded a strong positive signal for delta-9-tetrahydrocannabinol (THC) on urine drug test and exposure to THC oil was confirmed by the owner. Bloodwork revealed severe hyperlipidemia such that IV lipid emulsion was considered contraindicated. The dog was treated with a 3-hour ECT session, using charcoal hemoperfusion and hemodialysis in series. Neurologic signs improved during the session and mechanical ventilation was discontinued. Immediately after the session, the dog's mentation was significantly improved and seizures and hyperesthesia had ceased, although the dog remained moderately ataxic. The dog was hospitalized for 36 hours following the ECT session for continued monitoring. The dog fully recovered and was successfully discharged.

New or Unique Information Provided: To the authors' knowledge, this is the first published report to document ECT to treat THC intoxication in veterinary medicine. ECT may be considered as a treatment option for severe THC intoxication that is refractory to standard therapy or where severe hyperlipidemia precludes use of IV lipid emulsions.

KEYWORDS

charcoal hemoperfusion, hemodialysis, THC, toxicology

1 | INTRODUCTION

As legalization of marijuana becomes more widespread in the United States, marijuana intoxication is becoming a more frequent reason for dogs to present to emergency hospitals.[1] Due to the effect on the cannabinoid receptor CB1 and resulting inhibition of cyclic AMP and alterations to various ion channels, cannabinoids inhibit excitatory and inhibitory neurotransmitter release, resulting in a variety of neurologic and cardiovascular signs.[7] Many patients require only minimal intervention and may be managed on an outpatient basis or may be treated with supportive care.[1] However, an increase in the concentration of delta-9-tetrahydrocannabinol (THC) in marijuana products, the potential for ingestion of concentrated THC in baked goods, and increasing prevalence of recreational and medical grade synthetic THC products may result in more severe and potentially life-threatening clinical signs.[1,2] In severe intoxication where neurologic, cardiovascular, or respiratory effects are profound, treatment with IV lipid emulsion (ILE) therapy has been reported as a potential treatment option.[1,2] In situations where ILE is not an option due to hyperlipidemia or in circumstances where intoxication is severe and ILE is not effective, alternative treatments are needed, especially given the growing potential for more severe intoxication.

Hemodialysis has been reported to be effective at removing THC in people.[3] Given the lipophilic properties of THC and high protein binding, hemoperfusion may be another effective strategy at extracorporeal clearance.[4–6] In circumstances of life-threatening intoxication

Abbreviations: ECT, extracorporeal therapy; ILE, IV lipid emulsion; THC, delta-9-tetrahydrocannabinol.

requiring extracorporeal therapy (ECT), expediting drug clearance with the most efficient means possible is crucial, thus combining hemoperfusion and hemodialysis to amplify clearance warrants investigation.

To our knowledge, this is the first report of the use of ECT to treat THC intoxication in veterinary medicine. This paper serves to describe successful management of severe THC intoxication in a dog using hemoperfusion and hemodialysis in series.

2 | CASE SUMMARY

A 7-month-old female intact Labrador Retriever (17 kg) presented for acute onset of seizures. The owner noted that the dog was reluctant to go outside, was acutely ataxic, and hyperesthetic earlier that day. The owners observed seizure-like episodes characterized by a loss of consciousness and extreme tonicity lasting 15 to 30 seconds. No urination or defecation was observed during these episodes and the dogs was lethargic between episodes. At that time, there was no known potential for toxicant ingestion, obvious trauma, or previous history of neurologic disease. After multiple seizure-like episodes, the dog presented to the primary care veterinarian. Pertinent bloodwork findings included a decrease in total protein 52 g/L (5.2 g/dL; reference range 54–82 g/L [5.4–8.2 g/dL]) and globulin 17 g/L (1.7 g/dL; reference range 23–52 g/L [2.3–5.2 g/dL]). An hour later, the dog was discharged on phenobarbital* (1.9 mg/kg, PO, q 12 h), prednisone† (0.59 mg/kg, PO, q 12 h), and doxycycline‡ (5.9 mg/kg, PO, q 12 h).

The dog continued to have up to 20 seizures after discharge and presented to a tertiary referral center for further care, 3 hours after initial discharge. On presentation, the dog had a seizure, followed by altered and frantic mentation. Postictal physical exam showed the following abnormalities: a temperature of 37°C (98.6°F), heart rate 110/min, respirations of 40/min, miotic progressing to mydriatic pupils, nystagmus varying from horizontal to vertical, bilateral lateral strabismus, and absent gag. At this time, a Doppler blood pressure was 110 mm Hg and echocardiography revealed no abnormalities. Bloodwork was obtained on presentation. An arterial blood gas§ on flow by oxygen revealed the following abnormalities: pH 7.11 (reference range 7.4–7.54), $PaCO_2$ 67 mm Hg (reference range 18–32 mm Hg), sodium 135 mmol/L (reference range 140–152 mmol/L), and lactate 5.9 mmol/L (reference range 0.3–4.0 mmol/L). The glucose was normal at 5.44 mmol/L (98 mg/dL; reference range 3.89–7.27 mmol/L [70–131 mg/dL]) and the PaO_2 was 294 mm Hg. Packed cell volume was 0.42 L/L (42%), total plasma proteins were 70 g/L (7.0 g/dL), and the serum was noted to be very lipemic. Complete blood count¶ was unremarkable. A urine multidrug test# revealed a strong positive for THC and no other illicit substances (Figure 1). The owner then confirmed exposure to synthetic THC oil.

At presentation, the dog received midazolam‖ (0.5 mg/kg IV), but continued to be extremely anxious and dysphoric, with severe and frantic vocalization. Additional midazolam‖ (0.5 mg/kg IV) and levetiracetam** (60 mg/kg IV) were administered. Seizure activity persisted despite the above anticonvulsants and the dog was sedated with propofol†† (3 mg/kg IV), intubated, and mechanically ventilated.

FIGURE 1 Urine drug test of patient showing a strong positive for the cannabinoid delta-9-tetrahydrocannabinol (THC)

A bolus of isotonic crystalloid fluids‡‡ (29 mL/kg IV) was administered, followed by a second bolus an hour later (10 mL/kg). Phenobarbital[a] (4 mg/kg IV) was given as well as 7.5% hypertonic saline§§ (6 mL/kg IV) to treat potential increased intracranial pressure from recurrent seizure activity. An electroencephalogram showed rare epileptiform activity. Aspiration pneumonia was diagnosed based on thoracic radiographs that showed an interstitial to alveolar pattern in the left cranial lung lobe.

Intravenous lipid emulsion was not administered due to pre-existing severe lipemia. As such, ECT was initiated. A standard hemodialysis catheter¶¶ was sterilely placed in the right jugular vein. A 180-minute hemodialysis## session was performed, with a commercially available hemoperfusion cartridge‖‖ and hemodialysis filter*** connected in series (Figure 2). Ultrafiltration was matched with isotonic crystalloid fluids‡‡ to maintain neutral fluid balance. The total volume of blood processed during the session was 48 L (2.8 L/kg). Heparin sulfate††† (100 units/kg/h IV) was administered throughout the session for anticoagulation. The initial activated clotting time‡‡‡ was 189 seconds (reference range <120 s, target of 200–300 s during the session). The patient was monitored with continuous ECG§§§ and noninvasive blood pressure§§§ and remained hemodynamically stable throughout the session. One hour into the session, mechanical ventilation was discontinued and the level of sedation tapered. The patient's neurologic status progressively improved during the ECT (Figure 3). Hemoptysis was observed at the end of the session and was suspected to be secondary to excessive anticoagulation, based on an activated clotting time of 999 seconds. Protamine¶¶¶ (1.2 mg/kg, IV, over 1 h) was administered and the hemorrhage resolved completely without further intervention. At the end of the session, the dog was alert and responsive and there were no signs of seizure activity observed (Figure 4). The dog was able to walk and was admitted to the ICU for treatment of

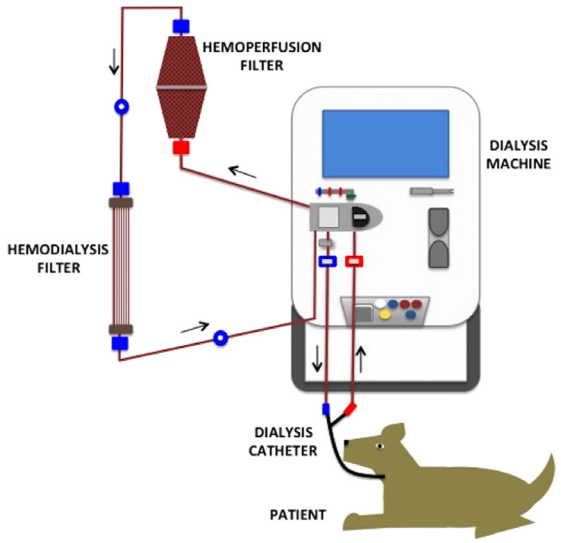

FIGURE 2 Setup of extracorporeal circuit showing the hemoperfusion cartridge and hemodialysis filter in series. Arrows indicate direction of blood flow

aspiration pneumonia with ampicillin-sulbactam[###] (22 mg/kg, IV, q 8 h), pantoprazole[||||||] (1 mg/kg, IV, q 12 h), and saline nebulization (q 6 h).

Six hours after ECT, the dog was quiet, alert, and slightly ataxic and ate readily. A CBC and biochemistry panel were unremarkable. The dog remained in the ICU for 36 hours after ECT on the following: maropitant[****] (1.2 mg/kg, IV, q 24 h), pantoprazole[||||||] (1.2 mg/kg IV q 12 h), ampicillin-sulbactam[###] (26 mg/kg, IV, q 8 h), and saline nebulization (q 6 h).

The dog was discharged on omeprazole[††††] (1.2 mg/kg, PO, q 24 h), amoxicillin-clavulonic acid[‡‡‡‡] (22 mg/kg, PO, q 12 h), and maropitant[****] (2.4 mg/kg, PO, q 24 h). One week after discharge, the dog was reportedly normal and doing well.

3 | DISCUSSION

Marijuana intoxication is a common reason for presentation to emergency hospitals. The onset of clinical signs may occur as soon as 30–60 minutes after ingestion.[7] Typical clinical signs include ataxia, hyperesthesia, depression, disorientation, mydriasis, urine dribbling, and hypothermia.[7] Less frequently signs such as tremors, seizures, and vocalization may be seen.[7] Deaths in dogs have been reported after consumption of baked goods made with THC butter.[1] A recent publication describes a mass intoxication in people from a "ultrapotent" synthetic cannabinoid that is 85 times as potent as delta-9-THC, resulting in "zombielike" behavior.[8,9] Synthetic cannabinoids are reportedly the fastest growing class of the new psychoactive substances, according to a recent United Nations Office on Drugs and Crime report.[§§§§] As

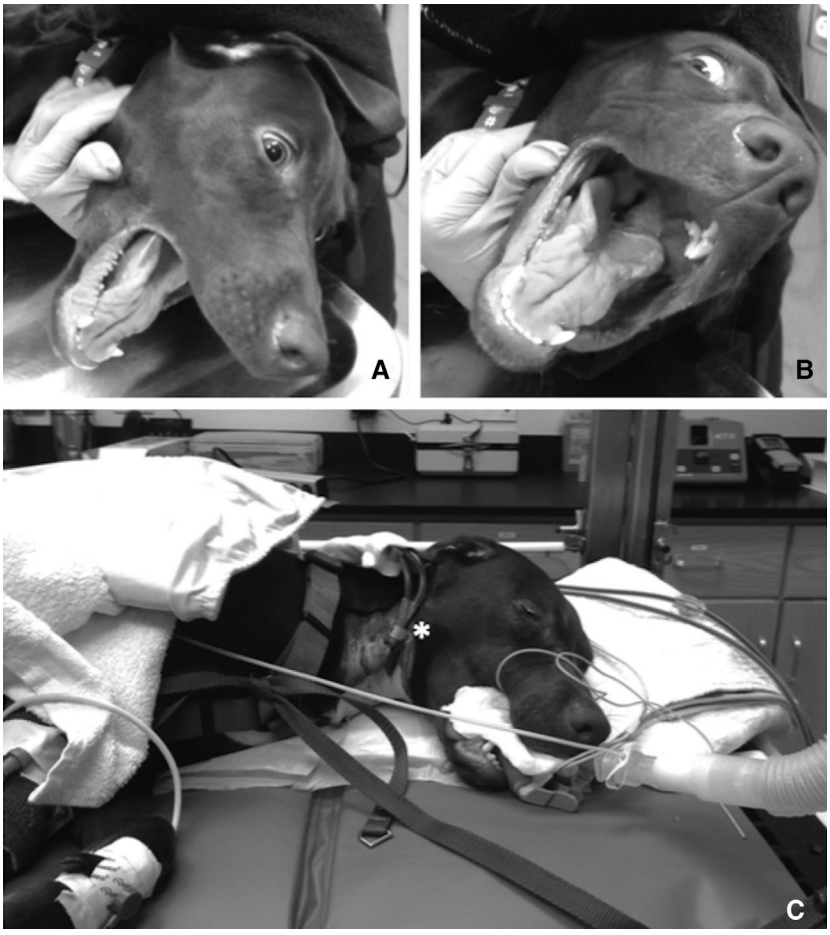

FIGURE 3 Patient before (A and B) and during (C) extracorporeal session for cannabinoid intoxication. At presentation, the patient was mentally inappropriate, with frantic vocalization and mydriasis (A and B). Ventral strabismus, nystagmus, and seizure activity were also observed at this time. As the patient was refractory to midazolam and levetiracetam, propofol was administered and mechanical ventilation initiated (C). Extracorporeal therapy was started with the patient mechanically ventilated (C). The dialysis catheter is marked with an asterisk (*)

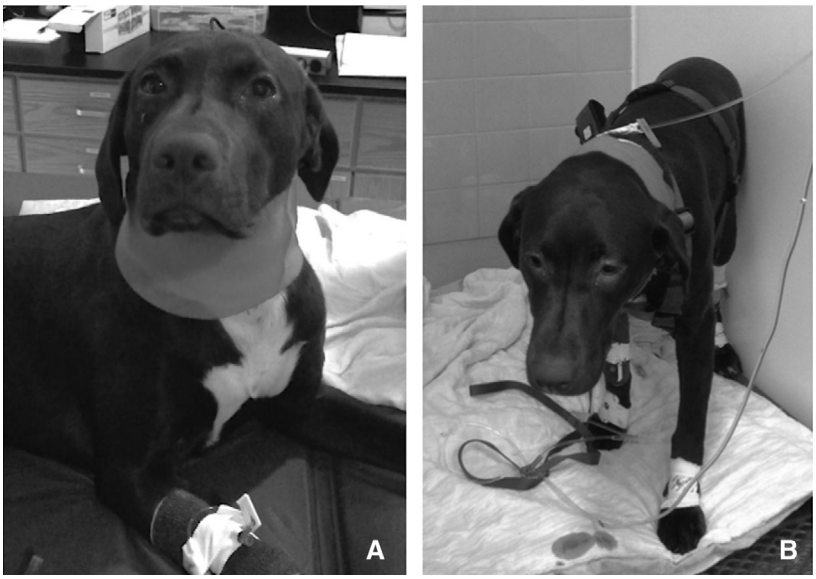

FIGURE 4 Patient immediately at the end of the extracorporeal session for cannabinoid intoxication, showing successful extubation and improvement of neurologic function (A). Patient upon admission to the ICU after the extracorporeal session, ambulatory, and mentally appropriate (B)

concentrated THC products become increasingly available and legalization increases the prevalence of marijuana products, patients may present with more severe intoxication and significant clinical signs.

Diagnosis is often made based on clinical signs and, ideally, confirmation by the owner of potential exposure. However, as in this case, diagnosis is not uncommonly complicated by owner reluctance to admit exposure or a client not knowing of the presence of cannabinoids in the household. On-site urine drug testing may be used to try to confirm a suspected intoxication, as this method is inexpensive, rapid, and readily available. Urine drug tests are designed for use in people, who metabolize THC into smaller and more stable compounds than canines, making it more difficult to detect in dogs.[10] Additionally, the sample must be properly handled and a sufficient amount of toxin must be present in the urine in order to potentially obtain positive results. Because of these factors, results of urine drug testing should be interpreted cautiously, with weight placed on clinical suspicion and diagnostics to rule out other potential causes.[10]

A large proportion of patients require only minimal intervention and may be managed on an outpatient basis or may be treated with supportive care.[1] In severe intoxication where neurologic effects are profound, treatment with ILE therapy is a potential option.[2,11] Hyperlipidemia is a potential consequence of ILE, thus it was not considered a valid treatment option in this patient that was already hyperlipidemic.[12]

Extracorporeal therapies such as hemodialysis or hemoperfusion may be considered in a variety of intoxications. The potential benefit of ECT must be weighed against the potential risks, costs, and availability of ECT. Additionally, consideration should be first given to an alternative therapy, such as an antidote or ILE, or supportive care in situations of mild intoxication. Hemodialysis utilizes a filter that allows movement of small molecules through a semipermeable membrane and may be utilized to correct acid base abnormalities and electrolyte derangements and clearance of uremic toxins in acute kidney injury, as well as exogenous toxin clearance. In veterinary medicine, hemoperfusion most frequently consists of a charcoal cartridge that indiscriminately binds larger and more protein-bound molecules. Depending on the toxin, these modalities may be used individually or in series to attempt to maximize exogenous clearance.

Hemodialysis has been documented to cause a decrease in whole blood concentrations of THC in people.[3] In this report, a chronic and heavy cannabis smoker required hemodialysis for terminal renal insufficiency and early THC withdrawal effects were seen 3 hours into treatment. The majority of the decrease in whole blood THC concentrations occurred in the first 2 hours of treatment; however, signs of withdrawal were not observed until 3 hours of treatment. The baseline THC concentration was 15.6 μg/L and decreased to 7.1 μg/L at the end of the 3.5-hour session. With our case, blood THC concentration levels were unable to be obtained, but significant improvement of clinical signs was seen during the 3-hour session. The rapidity of clinical change in our patient compared to that of the human report may reflect a difference in metabolism between dogs and humans, may be a reflection of the difference between intoxication and chronic use, or may suggest a more potent impact on drug clearance with the addition of hemoperfusion.

Lipophilic compounds or drugs that are highly protein bound are more likely to be cleared by hemoperfusion than by hemodialysis.[4] Because of the size of protein, protein-bound drugs will not readily diffuse across the dialysis filter and thus only unbound drug is removed. As hemoperfusion relies on adsorption, lipophilic or protein-bound compounds are more effectively removed. The protein binding of THC in dogs has been previously reported to be 97% and it is very lipophilic, suggesting hemoperfusion may be more effective than hemodialysis at THC clearance.[5,6] However, in toxins with a volume of distribution greater than 1 to 2 L/kg, hemoperfusion may have limited benefit. The volume of distribution of THC in the central compartment has been reported to be 1.31 L/kg in dogs.[6] Obtaining blood samples to measure THC concentrations pre- and posthemoperfusion cartridge and hemodialysis filter would be helpful in determining the contribution each device had on drug clearance. We attempted to obtain

pre- and posttreatment THC metabolite concentrations, but unfortunately the samples had degraded due to inadequate handling. It should be noted that THC is not stable and it adheres to glass and rubber stoppers, thus collection of blood or urine for testing should be carefully handled and results interpreted cautiously.[6,¶¶¶¶]

The endogenous clearance of a drug is an important consideration prior to initiating ECT to ensure that ECT will have a clinically significant impact.[4] The half-life of intravenously administered THC in dogs is reported to be 1.24 days.[6] It is important to note that gastrointestinal absorption is unpredictable and undergoes a first-pass effect.[7] Additionally, other metabolites that could contribute to clinical signs may be present. Although the drug clearance could not be measured in this patient and thus the exogenous clearance could not be determined, given the rapid change in clinical signs one can infer that cannabinoid clearance was largely enhanced by extracorporeal methods.

There are multiple important patient considerations when deciding to initiate ECT, in addition to cost and availability. In veterinary medicine, the size of patients can create a challenge, as even the smallest ECT components require a large amount of blood to be in the extracorporeal circuit. For example, in this patient, the following priming volumes required were as follows: blood circuit 75 mL, hemoperfusion cartridge 140 mL, and hemodialysis filter 83 mL, resulting in a total extracorporeal volume of 298 mL. Given the size (17 kg) and the relative hemodynamic stability of the patient described in this study, this volume was not problematic. However, a smaller patient may not tolerate this extracorporeal volume and techniques such as blood priming may be required. Coagulation within the extracorporeal circuit may be seen, particularly with hemoperfusion, so anticoagulation with heparin or citrate is required.[4] Close monitoring of the patient's coagulation and titration of the anticoagulant is compulsory; however, even despite this vigilance excessive anticoagulation may be seen, as occurred in this patient. Reversal of heparin with protamine or of citrate with calcium may be used if necessary.[13,14] In this patient, resolution of hypocoagulability based on clinical control of hemorrhage was achieved with administration of protamine and no further treatment was required.

This report suggests that ECT may be considered as a treatment in severe THC intoxication in situations where ILE is not an option or is not sufficient in improving clinical signs; however, further studies are needed.

CONFLICT OF INTERESTS

The authors declare no conflict of interests.

ENDNOTES

* Phenobabitone, Qualitest Pharmaceuticals, Huntsville, AL.

† Deltasone, West-Ward, Eatontown, NJ.

‡ Vibramycin, Heritage Pharmaceuticals, Eatontown, NJ.

§ Gem Premier 3000, Instrumentation Laboratory, Bedford, MA.

¶ HemaTrue, Heska, Loveland, CO.

Qtest, Qtest Inc., Linden, NJ.

‖ Versed, West-Ward, Eatontown, NJ.

** Keppra, X-Gen Pharmaceuticals, Big Flats, NY.

†† Propofol, Hospira, Lake Forest, IL.

‡‡ Vetivex, Dechra, Overland Park, KS.

§§ HTS, Vedco, St. Joseph, MO.

¶¶ 11.5 Fr x 20 cm Hemo-Cath, MedComp, Braunfels, Germany.

Phoenix X36, Gambro, Deerfield, IL.

‖‖ Adsorba 150C hemoperfusion cartridge, Gambro, Hechingen, Germany.

*** F160 NR Optiflux capillary dialyzer, Fresenius Medical Care, Waltham, MA.

††† Heparin sulfate, Hospira, Lake Forest, IL.

‡‡‡ ACT II, Medtronic, Minneapolis, MN.

§§§ Datascope Spectrum, Mindray, Mahwah, NJ.

¶¶¶ Protamine, Fresenius Kabi, Lake Zurich, IL.

Unasyn, AuroMedics Pharmacy, Dayton, NJ.

‖‖‖ Protonix, Wyeth Pharmaceuticals, Philadelphia, PA.

**** Cerenia, Pfizer, New York, NY.

†††† Prilosec, Glenmark Pharmaceuticals, Mahwah, NJ.

‡‡‡‡ Clavamox, Zoetis, Florham Park, NJ.

§§§§ World drug report 2015. Vienna: United Nations Office on Drugs and Crime.

¶¶¶¶ Cowan D, Osselton D, Robinson, S. Drug Testing, Foresight Brain Science, Addiction and Drugs project. 2006.

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REFERENCES

1. Meola S, Tearney CC, Haas SA, et al. Evaluation of trends in marijuana toxicosis in dogs living in a state with legalized medical marijuana: 125 dogs (2005–2010). *J Vet Emerg Crit Care*. 2012;*22*:690-696.
2. Williams K, Wells RJ, McLean MK. Suspected synthetic cannabinoid toxicosis in a dog. *J Vet Emerg Crit Care*. 2015;*25*:739-744.
3. Laprevote V, Gambier N, Cridlig J, et al. Early withdrawal effects in a heavy cannabis smoker during hemodialysis. *Biol Psychiatry*. 2015;*77*:e25-e26.
4. Ghannoum M, Bouchard J, Nolin T, et al. Hemoperfusion for the treatment of poisoning: technology, determinants of poison clearance, and application in clinical practice. *Semin Dial*. 2014;*27*:350-361.
5. Ashton C. Pharmacology and effects of cannabis: a brief review. *Br J Psychiatry*. 2001;*178*:101-106.
6. Garrett E, Hunt C. Pharmacokinetics of delta-9-tetrahydrocannabinol in dogs. *J Pharm Sci*. 1977;*66*:395-407.
7. Bischoff K. Toxicity of drugs of abuse. In: Gupta R, ed. *Veterinary Toxicology: Basic and Clinical Principles*. Waltham, MA: Elsevier; 2012:470-473.
8. Adams AJ, Banister SD, Irizarry L, et al. 'Zombie' outbreak caused by the synthetic cannabinoid AMB-FUBINACA in New York. *N Engl J Med*. 2017;*376*:235-242.
9. Banister SD, Longworth M, Kevin R, et al. Pharmacology of valinate and tert-leucinate synthetic cannabinoids 5F-AMBICA, 5F-AMB, 5F-ADB, AMB-FUBINACA, MDMB- FUBINACA, MDMB-CHMICA, and their analogues. *ACS Chem Neurosci*. 2016;*7*:1241-1254.
10. Teitler J. Evaluation of a human on-site urine multidrug test for emergency use with dogs. *JAAHA*. 2009;*45*:59-66.
11. Fitzgerald KT, Bronstein AC, Newquist KL. Marijuana poisoning. *Top Companion Anim Med*. 2013;*28*:8-12.

12. Fernandez AL, Lee JA, Rahilly L, et al. The use of intravenous lipid emulsion as an antidote in veterinary toxicology. *J Vet Emerg Crit Care*. 2011;*21*:309-320.
13. Vagianos C, Steen S, Masson P, et al. Reversal of lethal citrate intoxication by intravenous infusion of calcium. An experimental study in pigs. *Acta Chir Scand*. 1990;*156*:671-675.
14. Schulman S, Bijsterveld N. Anticoagulants and their reversal. *Trans Med Rev*. 2007;*21*:37-48.

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