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Toxicity, outcome, and management of anthracycline overdoses in 16 dogs

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Abstract

Background: Despite multiple reports of chemotherapy overdoses (ODs) in human and veterinary medicine, anthracycline ODs have been described infrequently.

Hypothesis/Objectives: Describe toxicities, treatments, and overall outcome after anthracycline OD in dogs.

Animals: Twelve mitoxantrone (MTX) and 4 doxorubicin (DOX) ODs were evaluated.

Methods: Multicenter retrospective analysis. The American College of Veterinary Internal Medicine oncology and internal medicine listservs were solicited for cases in which a chemotherapy OD occurred.

Results: Sixteen anthracycline cases were collected. Anthracycline ODs occurred because of an error in chemotherapy preparation (n = 9), or dose miscalculation (n = 7). The overall median OD was 1.9× (range, 1.4-10×) the prescribed amount. Most ODs were identified immediately after drug administration (n = 11), and the majority of patients were hospitalized on supportive care (n = 11) for an average of 8 days (range, 3-34 days). Adverse events after the OD included neutropenia (94%), thrombocytopenia (88%), anemia (63%), diarrhea (63%), anorexia (56%), vomiting (38%), lethargy (31%), and nausea (25%). Two patients did not survive the OD. High grade neutropenia was common and did not appear to be mitigated by the administration of filgrastim.

Conclusions and Clinical Importance: All patients received supportive care after identifying the OD and death was uncommon. Further evaluation is needed to determine ideal therapeutic guidelines anthracycline OD.

KEYWORDS
canine, chemotherapy, doxorubicin, mitoxantrone, overdose

1 | INTRODUCTION

Adjuvant chemotherapy is used in human and veterinary medicine to treat patients with various types of neoplasia. Chemotherapy protocols are complex and commonly are given in a busy hospital

Abbreviations: ACA, aminocaproic acid; DOX, doxorubicin; G-CSF, granulocyte colony-stimulating factor; GI, gastrointestinal; MTX, mitoxantrone; OD, overdose; rhG-CSF, recombinant human G-CSF; TCP, thrombocytopenia; TPE, therapeutic plasma exchange; TXA, tranexamic acid.

environment, increasing the potential for errors.[1] In human medicine, computer order entry, improved infusion pump technologies, advanced IV workflow systems, specialty credentialing, and multiple double checks are instituted to help minimize possible errors. Despite these efforts, chemotherapy overdoses (ODs) still occur.[1] Inaccurate chemotherapy administration also occurs in veterinary medicine, despite the adoption of similar safety protocols.[2-9] Reports regarding the frequency and type of ODs are lacking in both human and veterinary medicine.

In veterinary medicine, doxorubicin (DOX) and mitoxantrone (MTX) are used to treat a variety of cancers including lymphoma, urothelial carcinomas, and apocrine gland anal sac adenocarcinomas, among others.[10-13] At established dosages, anthracyclines are generally well-tolerated in both humans and dogs, with dose limiting toxicities including myelosuppression, gastrointestinal (GI) abnormalities, and anorexia.[14-16]

Despite the complexity of chemotherapy administration and multiple reports of chemotherapy ODs in human and veterinary medicine, anthracycline ODs have been described infrequently. One case series of humans reported 3 patients with >10× OD of MTX where moderate nausea and vomiting, chills, and profound but reversible neutropenia and thrombocytopenia developed. No cardiotoxicity was identified and all patients survived.[17] A second case report described a 10× MTX OD in a 9-year-old child that resulted in inefficient cardiac hemoperfusion and a reversible decrease in fractional shortening of the left ventricle.[18] Two patients receiving a 5× and 2× DOX OD developed severe mucositis. No cardiac dysfunction was observed and with supportive care both patients recovered within 18-26 days, despite prolonged myelotoxicity.[14]

There are no published reports describing MTX ODs in veterinary patients, and few describing DOX ODs. Two separate case reports describe dogs that received 51 mg/m^2 and 45 mg/m^2 of DOX. These patients both developed vomiting, diarrhea, anorexia, thrombocytopenia, and neutropenia. With GI support, filgrastim, and antibiotics, both patients survived.[2,3] Given the paucity of information available, our goals were to describe the toxicities, treatments, and overall outcome of anthracycline ODs in a group of dogs with the goal of developing therapeutic guidelines.

2 | MATERIALS AND METHODS

Our study was performed as a multicenter retrospective analysis. The American College of Veterinary Internal Medicine oncology and internal medicine listservs were solicited for cases in which an anthracycline OD occurred. Data was collected using an electronic data capture platform (REDCap, Vanderbilt University, Nashville, TN) and included signalment information (breed, weight, date of birth), tumor type, chemotherapeutic agent administered, dosage (mg/m^2 or mg/kg), why the error occurred, type of practice where the error occurred (general practice or specialty practice), adverse events (AEs) observed and when they occurred, treatments administered and when they were initiated, and overall patient outcome. Prophylactic care was defined as treatment initiated before development of clinical signs, and symptomatic care was defined as treatment initiated after development of clinical signs. Adverse events were reported according to the Veterinary Cooperative Oncology Group—Common Terminology Criteria for AEs.[19] The duration of each AE was categorized by the submitting clinician as lasting: 0-6 hours, 6-12 hours, 12-24 hours, 24-48 hours, 2-3 days, 3-4 days, 4-5 days, 5-6 days, 6-7 days, or > 7 days. Chemotherapy OD was defined based on a modified definition used in humans: patients were included for analysis if dosage administration was ≥10% higher than prescribed.[1] The OD was reported as a ratio of administered drug dosage to intended dosage (eg, dog that received 10 mg/m^2 of MTX instead of the intended 5 mg/m^2 was classified as a 2× OD). If the intended dosage was not known, a presumptive dosage of 6 mg/m^2 for

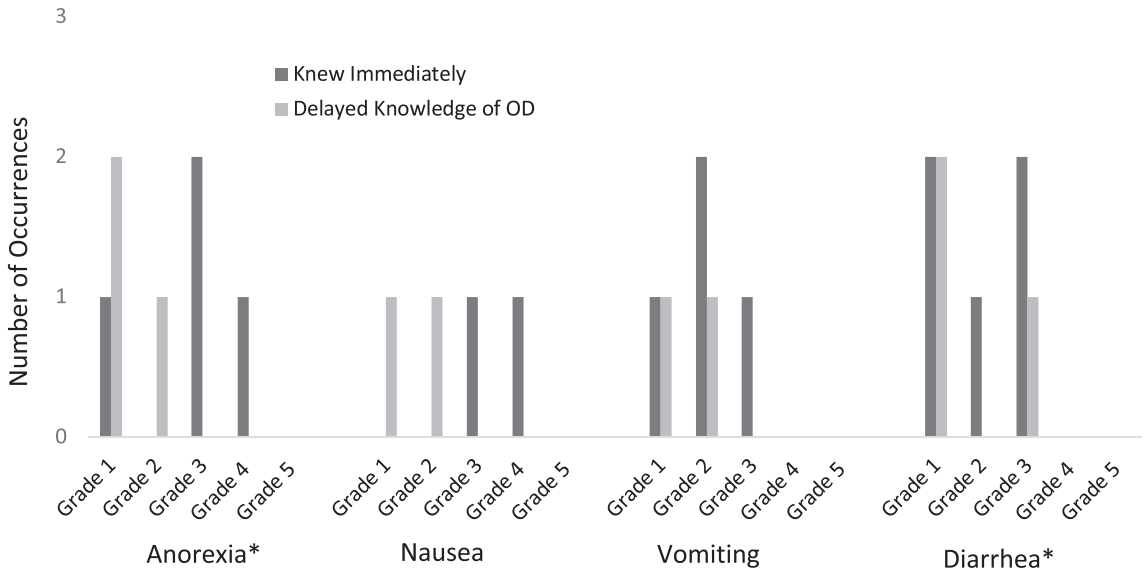

FIGURE 1 Summary of gastrointestinal adverse events following an anthracycline overdose (doxorubicin or mitoxantrone) in 16 dogs. Grade according to the VCOG-CTCAE; OD, overdose; *Two additional anorexia and diarrhea events were not graded

TABLE 1 Gastrointestinal medications administered to dogs after an anthracycline overdose

Gastrointestinal medications	Patients received prophylactically	Patients received supportively
Capromorelin (Entyce; Elanco, Greenfield, IN)	1	1
Dolasetron (Anzemet; Sanovi-Aventis, Bridgewater, NJ)	1	2
Famotidine (Pepcid; McNeal Health Care, Fort Washington, PA)	4	2
Fortiflora (Fortiflora; Nestle Purina PetCare Company, St. Louis, MO)	1	
Loperamide (Imodium A-D; Johnson & Johnson, New Brunswick, NJ)		1
Maropitant (Cerenia; Zoetis, Parsippany-Troy Hill, NJ)	6	5
Metoclopramide (Reglan; Watson, Arlington, VA)	2	4
Metronidazole (Flagyl; Sanofi lab, Bridgewater, NJ)	3	8
Mirtazapine (Remeron SolTab; Merck, Kenilworth, NJ)		2
Omeprazole (Prilosec; AstraZeneca, Wilmington, DE)	3	1
Ondansetron (Zofran; Glasko SmithKline, Philadelphia, PA)	2	2
Pantoprazole (Protonix; Pfizer, New York, NY)	1	2
Proviable (Proviable-DC; Nutramx Laboratories Veterinary Sciences, Inc, Lancaster, SC)		1
Ranitidine (Zantac; Sanofi, Bridgewater, NJ)		3
Sucralfate (Carafate; Aptalis Pharma Inc, Bridgewater, NJ)	1	5
Tylosin (Tylan; Elanco, Greenfield, IN)	1	1

MTX was used so as not to overestimate the OD (n = 3). It was assumed that DOX was prescribed at 30 mg/m^2 for dogs >15 kg, and 1 mg/kg for dogs ≤15 kg. Because of the small number of anthracycline ODs collected, descriptive statistical analysis, including measures of central tendency and variability, was completed. When the exact duration of an event was known (in days), it was reported as median and range. Otherwise, only range was reported.

TABLE 2 Antibiotics administered to dogs after an anthracycline overdose

Antibiotics	Patients received prophylactically	Patients received supportively
Amoxicillin (Amoxicillin; Zoetis, Parsippany-Troy Hill, NJ)	2	
Amoxicillin/clavulanic acid (Clavamox; Zoetis, Parsippany-Troy Hill, NJ)	1	5
Ampicillin sulbactam (Unasyn; Pfizer, New York, NY)	2	
Cefazolin (Ancef; Medline Industries, Inc, Northfield, IL)		1
Cefovecin (Convenia; Zoetis, Parsippany-Troy Hill, NJ)	1	1
Cephalexin (Keflex; Dista, Indianapolis, IN)	1	
Enrofloxacin (Baytril; Elanco, Greenfield, IN)	4	5

3 | RESULTS

Sixteen anthracycline ODs in dogs, including 12 MTX and 4 DOX, were collected. Patients were being treated for various neoplasms including lymphoma (n = 8), urothelial cell carcinoma (n = 4), prostatic carcinoma (n = 1), osteosarcoma (n = 1), apocrine gland anal sac adenocarcinoma (n = 1), and hemangiosarcoma (n = 1). Eight patients were receiving single agent protocols and 8 were receiving multiagent protocols. The most common breed was mixed (n = 7), followed by West Highland White Terrier (n = 2), and 1 of each of the following breeds: Beagle, Boxer, Labrador Retriever, Pekinese, Rat Terrier, Vizsla, and Yorkshire terrier. Weight was recorded in 10 patients: median, 10.9 kg (range, 5.98-31.4 kg). Date of birth was known for all patients but age at which the OD occurred was not collected.

Overdoses occurred because of an error in chemotherapy preparation in 9 patients, and a dose miscalculation in 7 patients. Most ODs occurred at specialty practices (n = 10). The median OD for all patients was 1.9× (range, 1.4-10×) the prescribed amount. The median MTX OD (n = 12) was 2× (range, 1.4-10×) with a median dosage of 10 mg/m^2 (range, 5-60 mg/m^2). The median DOX OD (n = 4) was 1.8× (range, 1.4-2.3x) with a median dosage of 44 mg/m^2 (range, 34-50 mg/m^2). Most ODs were identified immediately (n = 11), whereas 4 were recognized 6-7 days later after development of clinical signs. In 1 patient, the OD was identified after review of the medical record. Most patients were hospitalized (n = 11) for a mean of 8 days (range, 3-34 days) and all but 2 patients survived the OD.

3.1 | Gastrointestinal toxicity

Clinical signs for all patients included diarrhea (63%; median, grade II; range, grade I-III), anorexia (56%; median, grade II; range, grade I-IV), vomiting (38%; median, grade II; range, grade I-III), and nausea

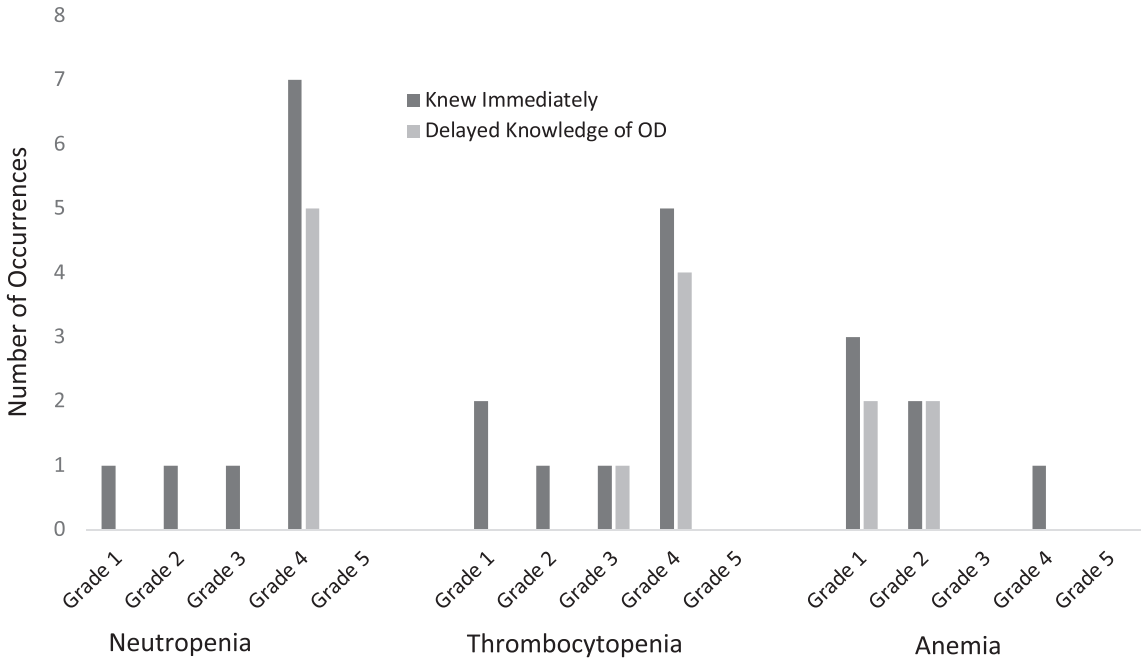

FIGURE 2 Summary of hematologic adverse events following an anthracycline overdose (doxorubicin or mitoxantrone) in 16 dogs. Grade according to the VCOG-CTCAE; OD, overdose

(25%; median, grade III; range, grade I-IV) (Figure 1 and Table S1). Two patients developed grade III ileus secondary to DOX OD.

Of the MTX OD patients that were identified immediately (n = 8), 4 received various prophylactic GI supportive medications (Table 1), and 4 did not. Two of the 4 patients that received prophylactic GI medications never developed GI signs. One patient developed grade I vomiting, diarrhea, and anorexia 2-3 days after the OD, which lasted >7 days. The other developed grade I diarrhea which started 6-12 hours after the OD, and persisted for 3-4 days. Two of the 4 patients not started on prophylactic GI supportive medications never developed GI clinical signs. The other 2 patients developed grade II vomiting or grade III anorexia (Table S1).

All DOX OD patients identified immediately (n = 3) received various prophylactic GI supportive medications (Table 1) but still experienced adverse GI effects (Table S1). In 2 patients, grade II and III vomiting and grade III and IV nausea were noted 2-3 days after the OD. Nausea persisted for 6 to >7 days and vomiting for 4-6 days. All 3 patients developed grade II or III diarrhea which developed 3-6 days after the OD. Diarrhea persisted for >7 days in 2 patients and 2-3 days in the other. Grade III or IV anorexia developed in 2 patients 24-72 hours after the OD and persisted for 5 to >7 days.

Anthracycline ODs in 3 patients were discovered 6-7 days later after development of GI signs (Table S1). All patients received GI supportive medications when the OD was discovered (Table 1). One patient developed grade I nausea that persisted for 2-3 days, grade I anorexia that persisted for 5-6 days, and grade I diarrhea that persisted for >7 days. A second patient developed grade I vomiting and anorexia of unknown duration. The final patient developed grade III diarrhea that persisted for >7 days.

3.2 | Bone marrow toxicity

Hematologic abnormalities developed in all patients and included neutropenia (94%), of which 12/15 (80%) were grade IV, thrombocytopenia (88%), and anemia (63%). In neutropenic patients, the median OD was 1.9× (range, 1.4-10×). Treatments for neutropenia are presented in Tables 2 and 4. A summary of the hematologic events observed, and specifically neutropenia, are presented in Figure 2, Tables 3, and S2. One patient had persistent neutropenia that did not respond to treatment. One additional patient did not develop neutropenia.

Twelve of 16 patients received filgrastim SC after the OD at a median dosage of 5 μg/kg (range, 4.7-10 μg) for a median of 5 days (range, 2-10 days). The duration of treatment was unknown for 2 patients. Seven of 12 received treatment prophylactically and 5/12 received treatment symptomatically. Of the patients that received filgrastim prophylactically, most received treatment 24 hours (n = 4) after the OD. The remaining patients received treatment immediately after (n = 1), 48 hours (n = 1), or 72 hours (n = 1) after the OD. Most patients that received treatment prophylactically (6/7) developed grade III (n = 1) or grade IV (n = 5) neutropenia 3-7 days after the OD with a median duration of 13 days (range, 1-66 days; Table 3).

All patients that received filgrastim symptomatically (n = 5) developed grade IV neutropenia that occurred 3-7 days after the OD. These patients received filgrastim 8-14 days post-OD for a median of 5 days (range, 2-7 days). The duration of filgrastim for 1 patient was unknown. The duration of neutropenia was known for 4/5 patients (median, 6 days; range, 3-27 days). The other patient had neutropenia for >7 days, but the exact duration was unknown (Table 3). Of the patients that never received filgrastim (n = 4), all developed neutropenia (grades I, II, IV).

TABLE 3 Impact of filgrastim on development of neutropenia after anthracycline overdose in dogs

	MTX (n = 12)						DOX (n = 4)					
Grade[a]	Prophylactic Filgrastim (n = 5)	Mean time to neutropenia (days)	Mean duration of neutropenia (days)	No Prophylactic filgrastim (n = 7)	Mean time to neutropenia (days)	Mean duration of neutropenia (days)	Prophylactic Filgrastim (n = 2)	Mean time to neutropenia (days)	Mean duration of neutropenia (days)	No Prophylactic filgrastim (n = 2)	Mean time to neutropenia (days)	Mean duration of neutropenia (days)
I				1	> 7	>7						
II										1	>7	>7
III	1	6-7	>7									
IV	3	6-7	>7	6	5.5	>7	2	3-4	3	1	6-7	2-3
V												
No neutropenia	1		N/A									

[a]Grade according to the VCOG-CTCAE.
Abbreviations: DOX, doxorubicin; MTX, mitoxantrone.

The exact duration of neutropenia was known for 2 patients (8 and 14 days) and was described as >7 days for the remaining 2 (Table 3).

No difference in duration of hospitalization was found for patients that received filgrastim compared to those that did not. Patients that received filgrastim and were hospitalized (9/12), remained hospitalized for a median of 5 days (range, 3-34 days). Of the patients that never received filgrastim, 2/4 were hospitalized for a median of 6 days (range, 4-7 days).

Four MTX OD patients became febrile with a median temperature of 40.1°C (range, 39.7-41°C). At the time of fever, 1 had grade I neutropenia that lasted 14 days, whereas the other 3 had grade IV neutropenia that lasted a median of 13 days (range, 5-66 days). Two were receiving prophylactic antibiotics when they became febrile (Table 2) but not GI medications. Of these dogs, 1 became febrile 10 days after the OD and was never hospitalized. The other received filgrastim prophylactically for 5 days starting 24 hours after the OD, but became febrile 21 days after the OD, was subsequently hospitalized, and did not survive. The ODs of the other 2 patients were identified 7 days post-OD. One presented for grade I nausea, diarrhea, anorexia, and grade II lethargy. The second presented for grade I vomiting, anorexia, lethargy, and diarrhea (grade unknown). Both were found to be febrile and neutropenic on presentation and were subsequently hospitalized for 6 days. Both patients received filgrastim, 1 for 5 days starting 11 days after the OD, and the other when the OD was identified (unknown duration).

Thrombocytopenia was noted in 88% (14/16) of patients with a median OD of 1.9× (range, 1.4-10×; Figure 2 and Table S2). In 13 patients, this abnormality was noted 6-7 (n = 4) or >7 (n = 9) days after the OD occurred. Thrombocytopenia was noted 12-24 hours after the OD in the remaining patient. Thrombocytopenia persisted for >7 days in 11 patients, and the exact duration was known for 7/11 (median, 34 days; range, 21-66 days). Of the 14 patients with thrombocytopenia, 3 with grade IV thrombocytopenia received treatment. Two received whole blood transfusions; the duration of thrombocytopenia was >7 days in 1 patient, and never resolved in the other patient. The third patient received aminocaproic acid (ACA) and tranexamic acid (TXA) of unknown dose and frequency, and the duration of thrombocytopenia was >7 days. Two patients, 1 DOX 1.4× OD and 1 MTX 1.6× OD, did not develop thrombocytopenia.

Median grade II anemia (range, grade I-IV) occurred in 10 patients with a median OD of 2× (range, 1.5-10×; Figure 2 and Table S2). Most patients (n = 6) developed anemia >7 days after the OD. One developed anemia 12-24 hours after the OD; 2 additional patients developed anemia between 2 and 7 days (time to anemia development was unknown for 1 patient).

3.3 | Other toxicities

Five patients experienced lethargy (31%; median grade, II; range, grade I-IV). Lethargy developed 3 to >7 days after the OD (n = 4) and persisted for 3-5 days (n = 2). Lethargy did not resolve in 1 patient (timing of lethargy development and duration was unknown for

TABLE 4 Other treatments administered to dogs after an anthracycline overdose

Medications	Patients received prophylactically	Patients received supportively
Aminocaproic acid (Amicar; Amneal Pharmaceuticals, Bridgewater, NJ)		1
Charcoal (Activated) (Actidose-Aqua; Perrigo Company, Allegan, MI)	1	
Coenzyme Q10 (Ubiquinol; Kaneka Corporation, Pasadena, TX)	1	
Dexrazoxane (Zinecard; Pfizer, New York, NY)	1	
Filgrastim (Neupogen; Amgen, Inc, Thousand Oaks, CA)	7	5
S-Adenosylmethionine (Denamarin; Nutramax Labs, Lancaster, SC)	2	
Therapeutic plasma exchange		1
Tranexamic acid (Cyklokapron; Pfizer, New York, NY)	1	
Whole blood transfusion		2

1 patient, and only time of development was known for 1 other patient).

A Boxer being treated for multicentric lymphoma received 10× the prescribed dosage of MTX. This patient was presented for seizures 4 days after the OD occurred. No GI toxicities were reported, but grade IV neutropenia and thrombocytopenia persisted for >7 days. Clinical sequelae of thrombocytopenia included petechiae and epistaxis. Alopecia of the hind limbs developed 39 days post-OD and persisted for several months. The patient also was diagnosed with chronic kidney disease 3 months after the OD, but survived the OD.

A second patient receiving a 2× OD of MTX developed renal failure 1.8 years after the OD and subsequently was euthanized. One patient that received a 1.6× OD of DOX developed alopecia, and another that received a 1.5× OD of DOX was reported to have long-term lethargy and inappetence up to 60 days after the OD. This owner elected to stop chemotherapy as a result.

Two patients were euthanized because of their OD. The first patient was a West Highland White Terrier being treated for urothelial cell carcinoma with MTX. A 2× OD was identified immediately after the fourth dose. Prophylactic cephalexin and filgrastim were prescribed, but the patient was not hospitalized. Grade II vomiting, managed with maropitant, developed 2-3 days after the OD. Melena, treated with loperamide, developed 14 days after the OD. Grade IV thrombocytopenia and anemia (noted 6 to >7 days post OD) were treated with whole blood and packed red blood cell transfusions, but did not resolve. As mentioned previously, this patient became febrile 21 days post-OD and subsequently was hospitalized for 34 days until the patient was euthanized because of unresolved adverse events 66 days post-OD.

TABLE 5 Treatment recommendations after moderate (2×-intended) anthracycline overdoses in dogs

Expected AEs	Treatment recommendations
Mitoxantrone	
Mild gastrointestinal effects	Supportive medications: • Antinausea medications • Appetite stimulants once nausea, vomiting, and diarrhea are controlled • H2 receptor antagonists or proton pump inhibitors • +/− IV Fluids, depending on severity of clinical signs
Severe neutropenia	• Broad-spectrum antibiotics started within 7 days of OD • +/− Filgrastim no sooner than 24 hours after OD
Severe thrombocytopenia	• Whole blood transfusions as needed • +/− Tranexamic acid • +/− Aminocaproic acid
Doxorubicin	
Severe diarrhea	Supportive medications: • Antidiarrheals/supportive antibiotics (metronidazole/tylosin) • Consider activated charcoal
Mild anorexia, nausea, vomiting	Supportive medications: • Antinausea medications • Appetite stimulants once nausea, vomiting, and diarrhea are controlled • H2 receptor antagonists or proton pump inhibitors • +/− IV Fluids, depending on severity of clinical signs
Severe neutropenia	• Broad-spectrum antibiotics started within 3 days of OD • +/− Filgrastim no sooner than 24 hours after OD
Severe thrombocytopenia	• Whole blood transfusions as needed • +/− Tranexamic acid • +/− Aminocaproic acid

Abbreviations: AEs, adverse events; OD, overdose.

The second patient received a 7.1× MTX OD. Despite pretreatment with maropitant, nausea developed 2 days post-OD and on presentation grade IV neutropenia was identified. These AEs were thought to be secondary to chemotherapy, but the OD was not identified at that time. Cefovecin and mirtazapine were prescribed. The patient showed no improvement and was hospitalized 5 days after the OD for grade II nausea, vomiting, and anorexia. Supportive care included IV fluids, enrofloxacin, and ondansetron. The patient developed dark stools and diarrhea 6 days after the OD and additional GI medications were started (sucralfate, ranitidine). The patient developed worsening neutropenia and grade IV thrombocytopenia 8 days post-OD. A blood transfusion was recommended, but the owner declined and elected euthanasia 8 days post-OD.

Other treatments administered prophylactically included s-adenosylmethionine and silybin, activated charcoal, and therapeutic

plasma exchange (TPE; Table 4). The patient that received TPE underwent 1 session 36-48 hours after the OD. This patient developed grade IV neutropenia 6-7 days after the OD, but no other GI or hematologic AEs were identified. The patient that received activated charcoal developed grade I vomiting, diarrhea, and anorexia 2-3 days after the OD which persisted for >7 days. Grade IV neutropenia and thrombocytopenia also occurred in this patient and lasted for >7 days.

Of the patients that were never hospitalized (MTX OD, 4; DOX OD, 1), all survived. The median OD was 1.8× (range, 1.4-10×). Four ODs were identified immediately, and these patients were started on prophylactic antibiotics (4/4), GI support (3/4) and filgrastim (2/4). One patient each had grade I or II diarrhea, or grade III anorexia which occurred from 6 hours to 7 days post-OD and all signs persisted >7 days. One patient had no GI signs, and 1 had ungraded anorexia. Grade I-IV neutropenia and grade I (n = 2), II, and IV thrombocytopenia occurred in 4 patients; 2 patients developed grade I anemia. Clinical signs persisted for an average of 11 days (range, 5-13 days).

4 | DISCUSSION

Our retrospective study describes the toxicities, treatments, and outcomes of dogs that experienced anthracycline ODs. In dogs, anthracycline dose limiting toxicities include vomiting, diarrhea, anorexia, and sepsis secondary to myelosuppression.[11,20] After a median anthracycline OD of 1.9× (range, 1.4-10×), >50% of patients experienced neutropenia, thrombocytopenia, anemia, diarrhea, and anorexia.

Only 2 case reports describing dogs with DOX ODs have been published in the veterinary literature, and we could not identify any MTX ODs reported in the literature. One OD occurred in a mixed breed dog with multicentric lymphoma that received single agent DOX chemotherapy (51 mg/m^2). This patient developed grade III regurgitation, diarrhea, anorexia, and thrombocytopenia, grade IV neutropenia, and grade I fever. The patient received IV fluids, prophylactic GI medications, filgrastim, and antibiotics. The systemic toxicity resolved by day 9 and this patient survived, but chemotherapy was discontinued.[2] The second DOX OD occurred in a poodle that received 42 mg/m^2 for treatment of periprostatic hemangiosarcoma. The OD was identified immediately, and the patient prophylactically received IV fluids, GI medications, antibiotics, hepatoprotectants, and granulocyte colony-stimulating factor (G-CSF). This patient was hospitalized for 13 days and developed hematuria, grade III GI toxicity, grade IV myelosuppression, and grade I alopecia, but survived the OD.[3]

The DOX ODs reported here had similar outcomes to the previously reported cases. The median dosage of DOX received was 44 mg/m^2 (range, 34-50 mg/m^2) and the most common AEs were severe diarrhea (grade III), neutropenia (grade IV), and thrombocytopenia (grade III-IV), consistent with known dose limiting toxicities of DOX.[3] All patients received fluid therapy and GI medications, and 3/4 received filgrastim. Despite the use of filgrastim, these patients still developed grade IV neutropenia. All patients survived the OD, and long-term AEs described were alopecia, prolonged lethargy, and inappetence. No cardiotoxicity was identified, but only 1 DOX patient had cardiac evaluation and the follow-up time was short (2 days). Previous studies have suggested cardiotoxicity develops after a median of 194 days (range, 50-928),[21] and thus cardiotoxicity may have been missed in this population. Because the known lethal dosage of DOX in dogs is 72 mg/m^2,[22] these outcomes are not surprising.

Published dosages of MTX range from 5 to 6 mg/m^2. Toxicity at this dosage is minimal (approximately 12% of patients), and can include vomiting, anorexia, diarrhea, lethargy, and sepsis secondary to myelosuppression.[12,20] An initial study evaluating the safety of MTX in beagle dogs reported the minimum lethal dosage to be 10.3 mg/m^2,[23] whereas an additional study described severe, life-threatening toxic effects and death in dogs receiving 6.5 mg/m^2 IV every 3 weeks.[20] Thus, it is suggested that MTX be administered at a maximum dosage of 6 mg/m^2.[20] Interestingly, dogs reported here received a median MTX dosage of 10 mg/m^2 and the most common AEs reported were severe neutropenia (grade IV), thrombocytopenia (grade IV) and mild anemia. Death occurred in 2 patients; 1 because of prolonged AEs, and the other because of severe chemotherapy toxicity, although the OD was not identified until after the patient's death. The patient with prolonged AEs received a dosage of 10.7 mg/m^2 (2× the prescribed amount), a known lethal dosage.[23] The prolonged neutropenia, thrombocytopenia, and anemia may be attributable to the MTX OD, or potentially to the development of auto-antibodies to G-CSF secondary to the use of filgrastim (recombinant human G-CSF [rhG-CSF]). Chronic neutropenia has been described after administration of rhG-CSF to normal dogs, suspected to be secondary to antibody-mediated neutralization of endogenous G-CSF.[24] Whether or not that effect contributed to this patient's prolonged neutropenia is unknown.

Because no published veterinary therapeutic guidelines exist regarding anthracycline ODs, a goal of our study was to develop treatment recommendations. Because of the retrospective nature of our study and the different treatments instituted, using this data to develop specific therapeutic guidelines proved challenging. However, it is recommended that anthracycline ODs be treated like other toxicities in veterinary medicine: prevention of further absorption, providing supportive treatment, and administering specific antidotes.[25] General considerations are outlined below and in Table 5.

4.1 | Prevention of absorption

To prevent absorption, TPE was performed in 1 patient after a 1.6× MTX OD. Although no GI AEs were noted, grade IV neutropenia developed. No studies have reported TPE for chemotherapy ODs in veterinary medicine, but several case reports describe its use for nonsteroidal anti-inflammatory drug toxicities.[26,27] In humans, TPE has been successful for accidental ODs of highly protein-bound chemotherapeutic agents such as vincristine, vinblastine, and cisplatin.[28,29] Although both DOX and MTX are highly protein bound,[30,31] the volume of distribution also is high: between 2.2 and 7.8 L/kg for DOX[32] and 26.6 ± 4.9 L/kg for MTX.[30] As the volume of distribution increases, the usefulness of TPE decreases. Typically, it is unsuccessful for treatment of ODs where

the volume of distribution of the drug is > 1-2 L/kg.[33] Therefore, TPE is not likely to be successful in the event of an anthracycline OD.

Activated charcoal was administered to 1 patient after a 2.8× OD of MTX. This patient developed grade I GI toxicity and grade IV myelotoxicity. Activated charcoal is used in humans for chemotherapy-induced diarrhea, and decreases the frequency and severity of diarrhea in children receiving irinotecan, cisplatin, and doxorubicin, or irinotecan and carboplatin.[34,35] Activated charcoal may help increase GI DOX clearance because approximately 50% of the administered dose is eliminated in the feces after biliary excretion.[36] Although the patient that received activated charcoal had grade I vomiting, diarrhea, and anorexia, no definitive conclusions can be made about its efficacy based on administration to a single patient.

4.2 | Prophylactic or symptomatic treatment

All patients in our study received prophylactic or symptomatic care after the OD, and 14/16 patients survived. Prophylactic and symptomatic care most commonly included antinausea medications, other GI supportive medications, antibiotics, and filgrastim (Tables 1, 2, 4 and Tables S1 and S2). Although small sample size prevented statistical evaluation, no difference in outcome was apparent between patients that received prophylactic treatment vs symptomatic treatment and patients had similar survival rates (8/10 for prophylactically treated patients vs 6/6 for symptomatically treated patients), average duration of AEs (23 days for prophylactically treated patients vs 14 days for symptomatically treated patients), and severity of AEs. Numerically, AEs were prolonged in the prophylactically treated group. These patients may have had more severe clinical signs associated with their OD regardless of when treatment was initiated, although magnitude of ODs was similar between groups (2× for prophylactically treated vs 1.9× for symptomatically treated). These results suggest a positive outcome is possible regardless of when treatment is started after an anthracycline OD of 1.9×.

Despite the frequent occurrence of thrombocytopenia, only 2 patients received whole blood transfusions and 1 patient received ACA and TXA for grade IV thrombocytopenia. These antifibrinolytics are commonly used in humans to prevent blood loss and to decrease transfusion requirements in patients with increased risk of bleeding.[37] They also have been successfully used for immune and nonimmune mediated thrombocytopenia,[38,39] and TXA currently is being studied for use in people receiving treatment for hematological malignancies.[40] In dogs, TXA improves clot strength in vitro, but the clinical effects of antifibrinolytic drugs are unclear.[41-43] The use of TXA has been described in a dog that received a dosage of 2303 mg/m^2 of cyclophosphamide over 21 days and developed severe pancytopenia. The patient was treated with antibiotics, 2 whole blood transfusions, G-CSF, and TXA and made a full recovery.[4] The patient in our study that received antifibrinolytic treatments was given TXA IV q8h while in the hospital and was started on PO ACA at discharge. This patient developed grade IV thrombocytopenia 6-7 days after the OD, which improved to grade II at discharge (11 days after the OD), and 2 weeks later thrombocytopenia had completely resolved. Based on this patient and the limited literature available, it is difficult to know the role of antifibrinolytics in patients that develop thrombocytopenia secondary to a chemotherapy OD, but their use may be considered in severely affected animals.

4.3 | Administering antidotes

Filgrastim (rhG-CSF) was used commonly in patients in our study, either prophylactically (7/16) or symptomatically (5/16). In humans, filgrastim causes a rapid increase in neutrophil count 4-5 hours after administration and decreases the duration of severe neutropenia in patients receiving chemotherapy to 1-2 days,[44-46] while having no impact on mortality.[47,48] One study evaluating recombinant canine G-CSF showed a reduction in duration of neutropenia (from 5 days to 2 days) in dogs treated with a standard dosage (5 mg/m^2) of MTX.[49] In our study, 60% of patients that received filgrastim developed neutropenia for >7 days (7/12), whereas 100% of patients that did not receive filgrastim developed neutropenia for >7 days (4/4). In addition, those that did not receive filgrastim were less likely to develop high grade neutropenia (2/4) than those that received treatment (11/12). Because of the known sensitivity of rapidly dividing myeloid cells to chemotherapy, it is recommended that G-CSF not be used until at least 24 hours after the administration of chemotherapy to prevent the development of prolonged neutropenia.[50-52] Most patients that received filgrastim prophylactically (6/7) were treated between 24 and 72 hours after the OD. One patient received treatment the day of the OD, but no difference in development or duration of neutropenia was appreciated.

It is difficult to understand why filgrastim did not have a clear effect on severity or duration of neutropenia. Potentially, recombinant canine G-CSF may be more beneficial for anthracycline-induced myelosuppression compared to filgrastim.[53] As previously discussed, when using filgrastim there is a risk of antibody production that can neutralize the product and cause severe neutropenia.[24] Given the small number of patients, it is difficult to draw definitive conclusions about the impact of filgrastim after an anthracycline OD.

One patient received dexrazoxane for cardioprotection after a 1.4× OD of DOX. Dexrazoxane has been shown to decrease cardiotoxicity associated with anthracycline administration by interfering with iron-mediated free radical formation and inducing degradation of topoisomerase IIb.[54] No reports of cardiotoxicity were identified among the patients in our study, but only 2 patients had cardiac evaluations and follow-up time was short. Our results suggest that the overall risk of cardiotoxicity with an anthracycline OD is low. However, the small case number, limited follow-up, and unknown cumulative DOX dose make true risk assessment difficult and the role of dexrazoxane in these cases is unknown.

Overdoses in our study occurred because of errors in chemotherapy preparation or because of miscalculations. This finding stresses the importance of establishing strategies to help prevent

chemotherapy errors. Many of the approaches employed in human medicine[1] should be adopted in veterinary medicine when administering chemotherapy to help improve the overall safety of patients. This approach includes multiple double check systems to ensure the dosage, drug, and patient are correct before administration; computer order entry to decrease potential errors involving legibility of written prescriptions; specialty credentialing for veterinarians and veterinary technicians so that these personnel have familiarity with chemotherapy drugs, common dosages, drug volumes, and administration safety; and finally, pharmaceutical labeling designed to help decrease the chance of incorrect drug administration.[1]

Our study had some limitations. We had a small number of patients, limiting statistical evaluation. Because of its retrospective nature, treatments and monitoring of OD patients were variable and therefore it is possible that AEs were not always accurately reported. The median OD in our study was 1.9× (range, 1.4-10×), and therefore the outcomes reported here are not necessarily representative of more severe ODs that may occur. Limitations also occurred in how information was collected because full records were not received for every patient. Therefore, instances occurred where grade or duration of AEs, and intended chemotherapy dosage, were not available. There also were limitations regarding the reported timeline of AEs because durations were collected as a range, potentially leading to underestimates of duration.

In conclusion, all patients received supportive care after identifying the OD and death was uncommon. High grade myelotoxicity was common and neither grade nor duration of neutropenia appeared to be mitigated by filgrastim. Further evaluation is needed to determine ideal therapeutic guidelines for treatment of anthracycline OD. Anthracycline ODs can lead to severe GI AEs and myelosuppression. Therefore, it is recommended that protocols be put in place to help prevent ODs from occurring.

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CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Authors declare no IACUC or other approval was needed.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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