TOXICOLOGY TALK

MEET THE AUTHOR

Tamara Foss, CVT
ASPCA Animal Poison Control Center
Urbana, Illinois

Tamara has been with the ASPCA Animal Poison Control Center since 2000. She earned her bachelor's degree in agriculture with an emphasis in animal health technology from Murray State University in Kentucky. Tamara especially enjoys the toxicology-, research-, and information technology–related aspects of her position at the ASPCA. She has a passion for greyhounds and is an active volunteer and foster for American Greyhound. Outside of work, she loves spending time with her greyhounds, especially helping her greyhound Callen have fun playing running games like lure coursing and straight racing.

Trazodone in Veterinary Medicine

BACKGROUND

Trazodone is a serotonin 2A antagonist and reuptake inhibitor that has been used in human medicine as a prescription therapy for depression, aggression, sleeplessness, and anxiety since 1981.[1–3] It is available in 50-, 100-, 150-, and 300-mg tablets as well as 150- and 300-mg extended-release tablets.[1] No products are labeled for veterinary use.

Trazodone selectively blocks serotonin reuptake, which enhances serotonin's effects.[4] It is an antagonist of 5-HT_{2A}, H1-histaminic, and α1-adrenergic receptors at low to moderate doses, resulting in various levels of sedation.[3–6] It can have hypotensive effects.[4] At higher doses, trazodone acts as a serotonin agonist, and serotonin syndrome can develop.[4,6] Trazodone also has anxiolytic properties, but the exact mechanism of action is unknown.[4]

USE IN VETERINARY MEDICINE

In 2008, Gruen and Sherman studied 56 dogs prescribed trazodone in combination with other primary behavior therapies and discovered that trazodone seemed to offer therapeutic benefit with relatively minimal adverse effects.[7] Since then, studies have investigated the benefit of trazodone in postorthopedic surgery treatment plans involving confinement to enhance calm behavior and reduce anxiety in hospitalized dogs. Trazodone has generally been shown to be beneficial and relatively safe. Adverse events associated with trazodone can be divided into behavioral and systemic signs. Adverse

Studies have investigated the benefit of trazodone to enhance calm behavior and reduce anxiety in hospitalized dogs.

shutterstock.com/Gabriel Scott

events previously reported in the literature include drugged or "spacy" behavior, drowsiness, panting, anxiety/restlessness/agitation, vomiting/gagging, behavioral change (counter surfing and trash raiding), excitation, sedation, increased hunger, colitis, and aggression (growling).[5,7,8]

In veterinary medicine, trazodone is generally dosed at 1.7 to 19.5 mg/kg/d on a daily or as-needed basis with immediate action (not extended-release) tablets and can be given with food.[1] When administered in combination with tricyclic antidepressants or selective serotonin reuptake inhibitors, it is recommended to begin dosing trazodone at 2 to 5 mg/kg and increase as needed to a maximum dose of 14 mg/kg/d.[1] Trazodone should be administered about an hour before potential anxiety-inducing stimuli, as its onset of action is approximately 30 to 60 minutes.[1,5] Gruen and colleagues reported owner-observed duration of effect lasting 4 hours or more.[5] The parent compound has an elimination half-life of approximately 7 hours in immediate-release tablets.[1] Trazodone undergoes extensive metabolism in the liver and is predominately excreted via the kidneys.[1,4]

EXPOSURE

Incidence and Clinical Signs

The ASPCA Animal Poison Control Center reported 417 incidences involving single-agent trazodone exposures in 379 dogs from 2009 to 2013.[1] In 104 dogs experiencing adverse effects, sedation and lethargy were reported in 43% of the dogs. Ataxia was reported in 16% and vomiting in 14%. Overall, lethargy, sedation, depression, somnolence, and subdued behavior are considered common signs of trazodone exposure.[9] Additional information on signs reportedly exhibited by dogs exposed to trazodone alone from January 2003 to November 2016 and the lowest dose at which each sign was seen is provided in TABLE 1.

Management

Decontamination measures are an important component of exposure management. Induction of emesis within 1 hour of exposure is recommended in asymptomatic patients if no contraindications to emesis exist.[9] Activated charcoal with sorbitol may be recommended in large exposures only.[9]

Treatment of trazodone overdose generally consists of symptomatic and supportive care. Although adverse effects are often reported, relatively few cases have involved serious signs and no deaths are attributed to trazodone exposure to date.[9] Special attention should be given to ensuring maintenance of cardiac output and being attentive to signs of hyperthermia or hypothermia and correcting as needed.[9,11] IV fluid therapy may be needed to maintain blood pressure.[6,9] Diazepam is the drug of choice for managing tremors or seizures, and atropine is suggested for treatment of bradycardia.[6,9]

Being aware of signs associated with serotonin syndrome is important as this can be a serious and potentially life-threatening condition to manage. Serotonin syndrome develops as a result of an overabundance of serotonin in the central nervous system.[6] It can be a risk in cases of exposure to high doses of trazodone.[1,4] Clinical signs of serotonin syndrome in dogs, in order of most to least common, include vomiting, diarrhea, seizures, hyperthermia, hyperesthesia, depression, mydriasis, vocalization, death, blindness, hypersalivation, dyspnea, ataxia/paresis, disorientation, hyperreflexia, and coma.[1] Cyproheptadine, a serotonin antagonist, helps combat serotonin syndrome signs.[6,11] Phenothiazines should be used cautiously because of potential hypotensive effects.[6]

TABLE 1 Signs Associated With Trazodone Exposure in Dogs[10]

SIGN	LOWEST DOSE (MG/KG) AT WHICH SIGN WAS SEEN
Lethargy	0.55
Depression/vomiting	1.35
Ataxia	1.7
Diarrhea	2.82
Hyperactivity	3.8
Hypotension	5.94
Hyperesthesia	6.06
Vocalization	6.6
Tremors	8.17
Disorientation	8.28
Tachycardia/hypertension	8.83
Hyperthermia	11.8
Collapse	12.99
Mydriasis/bradycardia	16.23
Seizure	78.7

Interaction With Other Drugs

Trazodone interacts with numerous drugs, and some of these interactions may have clinically significant effects. Of special interest are medications that may be strong inhibitors or inducers of cytochrome P450 3A4 (CYP3A4) isoenzyme, which is involved in trazodone metabolism.[4] Azole antifungals (eg, ketoconazole, itraconazole, fluconazole) and macrolide antibiotics (eg, erythromycin, telithromycin, clarithromycin) are CYP3A4 inhibitors and thus may enhance the effect of trazodone.[1,4] Carbamazepine, phenobarbital, phenytoin, rifampicin, and modafinil, which are CYP3A4 inducers, may decrease the effect of trazodone.[1,4,9]

Extreme caution should be used with concomitant trazodone and fluoxetine use and/or exposure as it is believed that fluoxetine may inhibit metabolism of trazodone.[1,4] Additionally, fluoxetine and other serotonergic medications (eg, paroxetine, sertraline, amitriptyline, clomipramine, amphetamines, dextromethorphan) as well as monoamine oxidase inhibitors (eg, phenelzine, amitraz, selegiline), metoclopramide, and tramadol, could heighten the risk of serotonin syndrome when combined with trazodone.[1,4,6,8]

Serotonin syndrome patients with severe cardiac disease or renal and/or hepatic function deficits should be monitored very closely and may merit additional treatment measures.[1]

Prognosis

The prognosis for patients exposed to trazodone is generally good, especially when serotonin syndrome has not developed. Signs generally resolve in 12 to 24 hours.[6] ■

References

1. Plumb DC. Trazodone HCl. In: *Veterinary Drug Handbook*. 8th ed. Ames: John Wiley and Sons; 2016.
2. Trazodone (Poisindex Managements). In: POISINDEX® System (electronic version). Greenwood Village, CO: Truven Health Analytics. Available at: micromedexsolutions.com. Accessed December 2016.
3. Gruen ME. Beyond the front line: trazodone and other ancillary treatments for anxiety. *Vet Med Forum* May 2012 cvm.ncsu.edu/wp-content/uploads/2015/06/Gruen_VetMedForum_May2012.pdf. Accessed December 2016.
4. McEvoy GK, ed. Trazodone. In: AHFS Drug Information 2014. Bethesda, MD: American Society of Health-System Pharmacists; 2014:2450-2454.
5. Gruen ME, Roe SC, Griffith E, et al. Use of trazodone to facilitate postsurgical confinement in dogs. *JAVMA* 2014;245:296-301.
6. Wismer TA. Antidepressant drug overdoses in dogs. *Vet Med* 2000;95(7):520-525.
7. Gruen ME, Sherman BL. Use of trazodone as an adjunctive agent in the treatment of canine anxiety disorders: 56 cases (1995-2007). *JAVMA* 2008;233:1902-1907.
8. Gilbert-Gregory SE, Stull JW, Rice MR, et al. Effects of trazodone on behavioral signs of stress in hospitalized dogs. *JAVMA* 2016;249:1281-1291.
9. ASPCA Animal Poison Control Center. Trazodone vet protocol. Unpublished data.
10. ASPCA Animal Poison Control Center. AnTox database. Unpublished data.
11. Wismer TA. Antidepressant drug overdoses. *Vet Tech* 2006;27(5):278-281.

Toxicology Talk is written and reviewed by members of the American Society for the Prevention of Cruelty to Animals (ASPCA) Animal Poison Control Center (APCC). The mission of the APCC is to help animals exposed to potentially hazardous substances, which it does by providing 24-hour veterinary and diagnostic treatment recommendations from specially trained veterinary toxicologists. It also protects and improves animal lives by providing clinical toxicology training to veterinary toxicology residents, consulting services, and case data review.

The ASPCA APCC includes a full staff of veterinarians, including board-certified toxicologists, certified veterinary technicians, and veterinary assistants, and its state-of-the-art emergency call center routinely fields requests for help from all over the world, including South America, Europe, Asia, and the Pacific Islands.

ASPCA ANIMAL POISON CONTROL CENTER 888.426.4435

NexGard®
(afoxolaner) Chewables

CAUTION: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

Description:
NexGard® (afoxolaner) is available in four sizes of beef-flavored, soft chewables for oral administration to dogs and puppies according to their weight. Each chewable is formulated to provide a minimum afoxolaner dosage of 1.14 mg/lb (2.5 mg/kg). Afoxolaner has the chemical composition 1-Naphthalenecarboxamide, 4-[5- [3-chloro-5-(trifluoromethyl)-phenyl]-4, 5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-N-[2-oxo-2-[(2,2,2-trifluoroethyl)amino]ethyl.

Indications:
NexGard kills adult fleas and is indicated for the treatment and prevention of flea infestations *(Ctenocephalides felis)*, and the treatment and control of Black-legged tick *(Ixodes scapularis)*, American Dog tick *(Dermacentor variabilis)*, Lone Star tick *(Amblyomma americanum)*, and Brown dog tick (*Rhipicephalus sanguineus*) infestations in dogs and puppies 8 weeks of age and older, weighing 4 pounds of body weight or greater, for one month.

Dosage and Administration:
NexGard is given orally once a month, at the minimum dosage of 1.14 mg/lb (2.5 mg/kg).

Dosing Schedule:

Body Weight	Afoxolaner Per Chewable (mg)	Chewables Administered
4.0 to 10.0 lbs.	11.3	One
10.1 to 24.0 lbs.	28.3	One
24.1 to 60.0 lbs.	68	One
60.1 to 121.0 lbs.	136	One
Over 121.0 lbs.	Administer the appropriate combination of chewables	

NexGard can be administered with or without food. Care should be taken that the dog consumes the complete dose, and treated animals should be observed for a few minutes to ensure that part of the dose is not lost or refused. If it is suspected that any of the dose has been lost or if vomiting occurs within two hours of administration, redose with another full dose. If a dose is missed, administer NexGard and resume a monthly dosing schedule.

Flea Treatment and Prevention:
Treatment with NexGard may begin at any time of the year. In areas where fleas are common year-round, monthly treatment with NexGard should continue the entire year without interruption.

To minimize the likelihood of flea reinfestation, it is important to treat all animals within a household with an approved flea control product.

Tick Treatment and Control:
Treatment with NexGard may begin at any time of the year (see **Effectiveness**).

Contraindications:
There are no known contraindications for the use of NexGard.

Warnings:
Not for use in humans. Keep this and all drugs out of the reach of children. In case of accidental ingestion, contact a physician immediately.

Precautions:
The safe use of NexGard in breeding, pregnant or lactating dogs has not been evaluated. Use with caution in dogs with a history of seizures (see **Adverse Reactions**).

Adverse Reactions:
In a well-controlled US field study, which included a total of 333 households and 615 treated dogs (415 administered afoxolaner; 200 administered active control), no serious adverse reactions were observed with NexGard.

Over the 90-day study period, all observations of potential adverse reactions were recorded. The most frequent reactions reported at an incidence of > 1% within any of the three months of observations are presented in the following table. The most frequently reported adverse reaction was vomiting. The occurrence of vomiting was generally self-limiting and of short duration and tended to decrease with subsequent doses in both groups. Five treated dogs experienced anorexia during the study, and two of those dogs experienced anorexia with the first dose but not subsequent doses.

Table 1: Dogs With Adverse Reactions.

	Treatment Group			
	Afoxolaner		Oral active control	
	N[1]	% (n=415)	N[2]	% (n=200)
Vomiting (with and without blood)	17	4.1	25	12.5
Dry/Flaky Skin	13	3.1	2	1.0
Diarrhea (with and without blood)	13	3.1	7	3.5
Lethargy	7	1.7	4	2.0
Anorexia	5	1.2	9	4.5

[1]Number of dogs in the afoxolaner treatment group with the identified abnormality.
[2]Number of dogs in the control group with the identified abnormality.

In the US field study, one dog with a history of seizures experienced a seizure on the same day after receiving the first dose and on the same day after receiving the second dose of NexGard. This dog experienced a third seizure one week after receiving the third dose. The dog remained enrolled and completed the study. Another dog with a history of seizures had a seizure 19 days after the third dose of NexGard. The dog remained enrolled and completed the study. A third dog with a history of seizures received NexGard and experienced no seizures throughout the study.

To report suspected adverse events, for technical assistance or to obtain a copy of the MSDS, contact Merial at 1-888-637-4251 or www.merial.com/NexGard. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at http://www.fda.gov/AnimalVeterinary/SafetyHealth.

Mode of Action:
Afoxolaner is a member of the isoxazoline family, shown to bind at a binding site to inhibit insect and acarine ligand-gated chloride channels, in particular those gated by the neurotransmitter gamma-aminobutyric acid (GABA), thereby blocking pre- and post-synaptic transfer of chloride ions across cell membranes. Prolonged afoxolaner-induced hyperexcitation results in uncontrolled activity of the central nervous system and death of insects and acarines. The selective toxicity of afoxolaner between insects and acarines and mammals may be inferred by the differential sensitivity of the insects and acarines' GABA receptors versus mammalian GABA receptors.

Effectiveness:
In a well-controlled laboratory study, NexGard began to kill fleas four hours after initial administration and demonstrated >99% effectiveness at eight hours. In a separate well-controlled laboratory study, NexGard demonstrated 100% effectiveness against adult fleas 24 hours post-infestation for 35 days, and was ≥ 93% effective at 12 hours post-infestation through Day 21, and on Day 35. On Day 28, NexGard was 81.1% effective 12 hours post-infestation. Dogs in both the treated and control groups that were infested with fleas on Day -1 generated flea eggs at 12- and 24-hours post-treatment (0-11 eggs and 1-17 eggs in the NexGard treated dogs, and 4-90 eggs and 0-118 eggs in the control dogs, at 12- and 24-hours, respectively). At subsequent evaluations post-infestation, fleas from dogs in the treated group were essentially unable to produce any eggs (0-1 eggs) while fleas from dogs in the control group continued to produce eggs (1-141 eggs).

In a 90-day US field study conducted in households with existing flea infestations of varying severity, the effectiveness of NexGard against fleas on the Day 30, 60 and 90 visits compared with baseline was 98.0%, 99.7%, and 99.9%, respectively.

Collectively, the data from the three studies (two laboratory and one field) demonstrate that NexGard kills fleas before they can lay eggs, thus preventing subsequent flea infestations after the start of treatment of existing flea infestations.

In well-controlled laboratory studies, NexGard demonstrated >97% effectiveness against *Dermacentor variabilis*, >94% effectiveness against *Ixodes scapularis*, and >93% effectiveness against *Rhipicephalus sanguineus*, 48 hours post-infestation for 30 days. At 72 hours post-infestation, NexGard demonstrated >97% effectiveness against *Amblyomma americanum* for 30 days.

Animal Safety:
In a margin of safety study, NexGard was administered orally to 8 to 9-week-old Beagle puppies at 1, 3, and 5 times the maximum exposure dose (6.3 mg/kg) for three treatments every 28 days, followed by three treatments every 14 days, for a total of six treatments. Dogs in the control group were sham-dosed. There were no clinically-relevant effects related to treatment on physical examination, body weight, food consumption, clinical pathology (hematology, clinical chemistries, or coagulation tests), gross pathology, histopathology or organ weights. Vomiting occurred throughout the study, with a similar incidence in the treated and control groups, including one dog in the 5x group that vomited four hours after treatment.

In a well-controlled field study, NexGard was used concomitantly with other medications, such as vaccines, anthelmintics, antibiotics (including topicals), steroids, NSAIDS, anesthetics, and antihistamines. No adverse reactions were observed from the concomitant use of NexGard with other medications.

Storage Information:
Store at or below 30°C (86°F) with excursions permitted up to 40°C (104°F).

How Supplied:
NexGard is available in four sizes of beef-flavored soft chewables: 11.3, 28.3, 68 or 136 mg afoxolaner. Each chewable size is available in color-coded packages of 1, 3 or 6 beef-flavored chewables.

NADA 141-406, Approved by FDA

Marketed by: Frontline Vet Labs™, a Division of Merial, Inc.
Duluth, GA 30096-4640 USA

Made in Brazil.

®NexGard is a registered trademark, and ™FRONTLINE VET LABS is a trademark, of Merial.
©2015 Merial. All rights reserved.

1050-4493-03
Rev. 1/2015

FRONTLINE VET LABS
A DIVISION OF MERIAL LIMITED