

Propofol

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Administration of propofol, an IV anesthetic, can result in dose-dependent effects, ranging from sedation to general anesthesia.

Formulations

Two formulations of propofol are available for veterinary use in the United States. Both are isotonic 1% (10 mg/mL) macroemulsions with 10% soybean oil, 2.25% glycerol, and 1.2% egg-lecithin. The pH is adjusted to approximately 7.5 with sodium hydroxide.

Because the 2 formulation labels differ only slightly, users must be aware of which propofol formulation has been selected.

The original formulation has no preservative and, given the medium used to solubilize propofol, the label recommends discarding the container within 6 hours of first use to minimize microbial or fungal contamination. Refrigeration is not recommended so as to prevent separation of active drug from the emulsion.

To reduce potential waste from incomplete use of an opened container of preservative-free propofol, 2% benzyl alcohol has been included in the new formulation, with a 28-day shelf life after initial use. This formulation is only approved for use in dogs; safety and efficacy studies in cats are ongoing. Because the 2 formulation labels differ only slightly, users must be aware of which propofol formulation has been selected.

Additional nonlipid-based formulations of propofol have been evaluated to a limited extent for use in several species and are available in Europe and Australia; macroemulsion products with varying preservatives are also available for use in humans in the United States.

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Some patients may withdraw limbs in reaction to a potential burning or painful sensation with propofol administration.

Administration

Either veterinary propofol formulation may be administered over 30 to 90 seconds IV for induction of anesthesia. A titrated dose of 6 to 10 mg/kg is recommended in healthy, unsedated animals. Dose reduction is suggested for compromised patients.

Both sedation (premedication) and the addition of benzodiazepines to anesthetic induction protocol often reduce the dose requirement (by 1–4 mg/kg) and have the potential to reduce costs associated with propofol administration. Slow administration (versus rapid bolus) of propofol is recommended to allow blood and brain concentrations of drug to equilibrate and minimize the likelihood of a relative overdose. Slow administration is not usually associated with excitement as with historic drugs; cardiovascular and respiratory effects are also minimized.

Indications & Duration of Action

Propofol is primarily indicated as an IV sedative to facilitate a short period of restraint for nonpainful or minor procedures (eg, ultrasound evaluation, bandage change, upper airway examination) or as an anesthetic induction agent to facilitate intubation before maintenance with inhaled anesthetics. However, because of its unique pharmacokinetic profile (including a short context-sensitive half-time in dogs), it may be given by repeated injection or continuous infusion to maintain total IV anesthesia without significantly prolonging recovery.

Propofol has also been used concurrently with inhaled anesthetic agents (partial IV anesthesia). Analgesic drugs (eg, opioids, α_2 agents) are recommended to reduce dose and/or provide analgesia when use is extended to painful procedures.



Propofol is metabolized and redistributed by the liver and extrahepatic sites, resulting in an ultrashort duration of action. The effective clinical duration of action during which a patient can be manipulated is typically <10 minutes. Complete recovery to ambulation occurs within 20 minutes (dogs) or 30 minutes (cats) after an anesthesia induction dose and is rapid, smooth, and excitement free. These properties also make propofol a good choice in patients with underdeveloped (eg, kittens, puppies) or impaired (eg, geriatric patients, those with a portacaval shunt) liver function. Puppy viability after cesarean section is reportedly better following the dam's anesthesia induction with propofol than with other injectable induction agents.

Propofol is considered appropriate for patients with CNS disease, including refractory seizures and raised intracranial pressure, as long as rises in CO₂ tension are minimized. The effects on intraocular pressure are more variable and potentially influenced by other drugs and changes in CO₂ tension. Propofol mediates CNS actions by facilitating

inhibitory transmission through postsynaptic activation of the GABA-A receptor chloride complex. It also inhibits NMDA subtype of glutamate receptor, slow calcium channels, and voltage-gated sodium channels.

Disadvantages & Adverse Effects

Some animals (7.5% of unpremedicated dogs) may withdraw their limb in response to propofol administration (presumably from a burning or painful sensation), but perivascular injection does not cause a local inflammatory reaction. An animal may show focal twitches or muscle fasciculations, which do not appear harmful but can be disruptive, especially if localized to the surgical site.

Cardiovascular depression may be observed when propofol is administered as an IV bolus. This is more likely in volume-depleted patients and those with underlying cardiovascular disease. Arterial hypotension, the most common cardiovascular effect reported, primarily results from a decrease in systemic vascular resistance, although negative inotropic effects have also been reported. Slow administration of the drug and prior administration of IV fluids (5–10 mL/kg balanced electrolyte solution over ≤5–10 minutes) can help reduce these effects. However, in certain patients (eg, those with significant mitral regurgitation or heart failure), fluid administration at this rate may be inappropriate and could preclude propofol use. Respiratory depression to the point of the apnea is the most common effect reported after administration and may be minimized by slow administration.

While propofol may be used repeatedly or by infusion in dogs, cats respond less predictably, presumably from hepatic enzyme saturation (limited ability to glucuronidate). Prolonged recoveries following propofol infusion, Heinz body anemia, general malaise, anorexia, and diarrhea have been reported with sequential daily administration in cats. Recent reports suggest that the magnitude of some of these changes may be dose related. Other considerations with the macroemulsion formulation include the potential to exacerbate hyperlipidemia (increase triglycerides) in certain disease states. In addition to life-threatening sepsis possibly resulting from microbial contamination of propofol, an increase in the incidence of wound infections has been reported with propofol use in dogs. These findings may have been confounded by the methodology for administration and storage of the preservative-free intralipid compound.

Drug Interactions

As mentioned, propofol is commonly used with IV fluids and adjunct drugs (eg, α_2 agonists, benzodiazepines, opioids). Combinations of ketamine and propofol are also used for anesthesia induction. While concurrent use of these drugs may reduce the dose requirement of propofol, combinations may increase the incidence of adverse effects. Cardiovascular effects tend to vary and should be weighed in patients with cardiovascular disease; bradycardia with concurrent use of opioids is a possible effect but easily mitigated by administration of an anticholinergic.

Consider This

Propofol is not considered an analgesic drug; it does, however, have the potential to cause adverse reactions in animals that are allergic to components of the emulsion (eg, soy, peanuts, egg protein). The volume of drug necessary for anesthesia induction is larger than required for other common anesthetic drug combinations (eg, ketamine-diazepam), which may be of practical consideration if an IV catheter has not been placed. While generally not considered cost prohibitive, an equivalent dose of propofol is more expensive than a combination of ketamine and diazepam.

Recently, propofol has come under scrutiny for its potential as a drug of diversion and abuse with reports of both accidental overdose and intentional suicide in humans. This has led the US Drug Enforcement Agency to consider whether to assign it a *scheduled drug* designation.

Cats may recover less predictably than do dogs with propofol administration.

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Advantages

Propofol offers bronchodilation, which may be useful in asthmatic patients and has no detrimental effects on mucociliary function. Its effects on splenic size are either better or no worse than other contemporary induction agents. It may be used to maintain anesthesia in patients with malignant hyperthermia as it doesn't trigger this syndrome. It may also be considered the anesthetic-induction agent of choice in healthy greyhounds. Propofol is reported to have antiemetic benefits in recovery in humans.



Costs associated with propofol may be offset by improved recovery time.

See **Aids & Resources**, back page, for references & suggested reading.

Find More



For more information on anesthesia see Dr. Khursheed Mama's **Endocrine & Anesthesia Protocols: An Exclusive Series** on cliniciansbrief.com/endocrine-anesthesia-series

Economic Impact

Although the cost of propofol is more than the most common alternative (ketamine-diazepam), it is likely that the drug costs are somewhat offset by improved recovery time and quality. Because of the advantages and generally manageable disadvantages, propofol is rapidly becoming the anesthetic induction agent of choice for healthy dogs and cats. ■ **cb**

TRIFEXIS®

(spinosad + milbemycin oxime)

Cheewable Tablets

Before using TRIFEXIS chewable tablets, please consult the product insert, a summary of which follows:

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

Indications:

TRIFEXIS is indicated for the prevention of heartworm disease (*Dirofilaria immitis*). TRIFEXIS kills fleas and is indicated for the prevention and treatment of flea infestation (*Ctenocephalides felis*), and the treatment and control of adult hookworm (*Ancylostoma caninum*), adult roundworm (*Toxocara canis* and *Toxascaris leonina*) and adult whipworm (*Trichuris vulpis*) infections in dogs and puppies 8 weeks of age or older and 5 pounds of body weight or greater.

Contraindications:

There are no known contraindications to the use of TRIFEXIS Chewable Tablets.

Warnings:

Not for human use. Keep this and all drugs out of the reach of children.

Serious adverse reactions have been reported following concomitant extra-label use of ivermectin with spinosad alone, one of the components of TRIFEXIS Chewable Tablets (see **ADVERSE REACTIONS**).

Precautions:

Treatment with fewer than 3 monthly doses after the last exposure to mosquitoes may not provide complete heartworm prevention (see **EFFECTIVENESS**).

Prior to administration of TRIFEXIS, dogs should be tested for existing heartworm infection. At the discretion of the veterinarian, infected dogs should be treated with an adulticide to remove adult heartworms. TRIFEXIS is not effective against adult *Dirofilaria immitis*. While the number of circulating microfilariae may decrease following treatment, TRIFEXIS is not indicated for microfilariae clearance. Mild, transient hypersensitivity reactions manifested as labored respiration, vomiting, salivation and lethargy, have been noted in some dogs treated with milbemycin oxime carrying a high number of circulating microfilariae. These reactions are presumably caused by release of protein from dead or dying microfilariae.

Use with caution in breeding females. The safe use of TRIFEXIS in breeding males has not been evaluated. Use with caution in dogs with pre-existing epilepsy. Puppies less than 14 weeks of age may experience a higher rate of vomiting.

Adverse Reactions:

In a well-controlled US field study, which included a total of 352 dogs (176 treated with TRIFEXIS chewable tablets and 176 treated with an active control), no serious adverse reactions were attributed to administration of TRIFEXIS chewable tablets. All reactions were regarded as mild.

In some cases, dogs vomited after receiving TRIFEXIS. To ensure heartworm prevention, observe your dog for one hour after administration. If vomiting occurs within an hour of administration, redose with another full dose.

Reactions that occurred at an incidence >2% (average monthly rate) within any of the 6 months of observation are presented in the following table:

Average Monthly Rate (%) of Dogs With Adverse Reactions

Adverse Reaction	TRIFEXIS Chewable Tablets*	Active Control Tablets*
Vomiting	6.13	3.08
Pruritus	4.00	4.91
Lethargy	2.63	1.54
Diarrhea	2.25	1.54

*n=176 dogs

In the US field study, one dog administered TRIFEXIS experienced a single mild seizure 2½ hours after receiving the second monthly dose. The dog remained enrolled and received four additional monthly doses after the event and completed the study without further incident.

Following concomitant extra-label use of ivermectin with spinosad alone, a component of TRIFEXIS, some dogs have experienced the following clinical signs: *trembling/twitching, salivation/drooling, seizures, ataxia, mydriasis, blindness and disorientation*. Spinosad alone has been shown to be safe when administered concurrently with heartworm preventatives at label directions.

In US and European field studies, no dogs experienced seizures when dosed with spinosad alone at the therapeutic dose range of 13.5-27.3 mg/lb (30-60 mg/kg), including 4 dogs with pre-existing epilepsy. Four epileptic dogs that received higher than the maximum recommended dose of 27.3 mg/lb (60 mg/kg) experienced at least one seizure within the week following the second dose of spinosad, but no seizures following the first and third doses. The cause of the seizures observed in the field studies could not be determined.

For technical assistance or to report an adverse drug reaction, call 1-888-545-5973. Additional information can be found at www.TRIFEXIS.com.

Post-Approval Experience (March 2012):

The following adverse reactions are based on post-approval adverse drug event reporting. The adverse reactions are listed in decreasing order of frequency: vomiting, depression/lethargy, pruritus, anorexia, diarrhea, trembling/shaking, ataxia, seizures, hypersalivation, and skin reddening.

Effectiveness:

Heartworm Prevention:

In a well-controlled laboratory study, TRIFEXIS was 100% effective against induced heartworm infections when administered for 3 consecutive monthly doses. Two consecutive monthly doses did not provide 100% effectiveness against heartworm infection. In another well-controlled laboratory study, a single dose of TRIFEXIS was 100% effective against induced heartworm infections. In a well-controlled six-month US field study conducted with TRIFEXIS, no dogs were positive for heartworm infection as determined by heartworm antigen testing performed at the end of the study and again three months later.

Flea Treatment and Prevention:

In a well-controlled laboratory study, TRIFEXIS demonstrated 100% effectiveness on the first day following treatment and 100% effectiveness on Day 30. In a well-controlled laboratory study, spinosad, a component of TRIFEXIS, began to kill fleas 30 minutes after administration and demonstrated 100% effectiveness within 4 hours. In field studies conducted in households with existing flea infestations of varying severity, flea reductions of 98.0% to 99.8% were observed over the course of 3 monthly treatments with spinosad alone. Dogs with signs of flea allergy dermatitis showed improvement in erythema, papules, scaling, alopecia, dermatitis/pyodermitis and pruritus as a direct result of eliminating the fleas.

Treatment and Control of Intestinal Nematode Infections:

In well-controlled laboratory studies, TRIFEXIS was ≥ 90% effective in removing naturally and experimentally induced adult roundworm, whipworm and hookworm infections.

NADA #141-321; Approved by the FDA

Manufactured for Elanco Animal Health
A Division of Eli Lilly & Co.
Lilly Corporate Center, Indianapolis, IN 46285

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EP086173AMD (V02-06-2012)