

Veterinary Hyperbaric Oxygen Therapy: A Critical Appraisal

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ISSUE

HYPERBARIC OXYGEN THERAPY (HBOT) IS A COMPARATIVELY NOVEL TREATMENT IN VETERINARY MEDICINE AND ONE THAT HAS GENERATED BOTH INTEREST AND CONTROVERSY.

- ▶ HBOT is equivalent to drug administration, albeit in the form of pure oxygen.
- ▶ Although there are associated adverse events and risks, there is also potential for clinical utility.
- ▶ Rapidly increasing use of HBOT in general and specialty veterinary practices worldwide warrants critical appraisal of the history of the modality; its therapeutic principles, safety, and efficacy; and its application in treating specific diseases.

ANSWER

HISTORY

HBOT is most notably related to diving medicine and decompression sickness in humans.¹ No published history of veterinary HBOT is available; however, based on the available human data, several specialty practices began employing the modality 2 decades ago using hyperbaric chambers intended for use in humans. The recent appearance of veterinary-specific chambers and more publicized cases has prompted increased use,² with dozens of chambers now positioned in veterinary facilities across the United States, including University of Florida and University of Tennessee. In addition, CE topics on HBOT use have been featured at major veterinary conferences.

PRINCIPLES & PHYSIOLOGY

HBOT increases the dissolved plasma oxygen content according to 3 main laws that describe the behavior of gases when exposed to alterations in pressure: Henry's, Fick's, and Boyle's (see **Laws of Gas Behavior**, next page).³ Understanding these principles is crucial to comprehending not only HBOT's mechanism of action but also its potential indications and contraindications.

HBOT = hyperbaric oxygen therapy

LAWS OF GAS BEHAVIOR³

- **Henry's Law:** The solubility of a gas is proportional to its pressure when in equilibrium with a liquid (ie, solubility coefficient).
- **Fick's Law:** The diffusion of a gas is proportional to the gas concentration gradient or difference in partial pressures of a gas across the tissue.
- **Boyle's Law:** With increasing pressure, the volume of a gas decreases proportionally.

In relation to HBOT, Henry's Law establishes that the higher the treatment pressure, the greater the amount of dissolved oxygen in the blood. Fick's Law explains the therapeutic potential of HBOT in chronic, nonhealing, and hypoxic wounds, as oxygen diffuses farther into tissues after leaving the capillaries and entering the interstitial fluid—fluid that would otherwise be oxygen deprived secondary to vascular compromise or local inflammation. Boyle's Law establishes that gas increases in volume in a fixed cavity if not allowed to exit and does so proportionally to the decrease in pressure, thus risking barotrauma in patients receiving a decompression protocol too rapidly.

Diffusion of oxygen into plasma, interstitial fluid, cytoplasm, and mitochondria is limited by the oxygen diffusion gradient, hemoglobin saturation, and amount of hemoglobin. Hemoglobin saturation is more than 97%, with typical oxygen concentrations (21%) at sea level (1 atmosphere absolute [ATA]); therefore, any additional hemoglobin saturation exerts minimal effect.⁴ However, freely dissolved plasma oxygen is significantly increased when inhaled oxygen is increased through delivery of pure oxygen and/or pressurization of inhalant gases.³ A commonly achieved treatment pressure of 100% oxygen at 2 ATA results in a 10-fold increase in plasma oxygen content over breathing air at sea level.⁵

The physiologic effects of HBOT have been well studied in humans and in laboratory animals. Observed changes include increased cellular energy (ie, via adenosine triphosphate) production via the presence of additional oxygen for phosphorylation, which is a limiting factor in the normal cellular environment.⁶ In

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addition, short-term sublethal oxidative stress produced by free oxygen species can result in a compensatory increase in production of endogenous intracellular antioxidants (eg, glutathione). HBOT induces vasoconstriction of arterioles and venules during hyperbaric sessions to reduce tissue and vasogenic edema while supplying adequate oxygen. HBOT also modulates the vasodilator nitric oxide following treatment.⁷ Secondary effects include anti-inflammatory, antimicrobial, and immunomodulatory, as well as angiogenic, effects.^{3,8}

Treatment Overview

There is a paucity of data about use of HBOT in veterinary medicine, and no randomized, controlled clinical trials for any condition have been published. Thus, veterinarians must rely on the comparatively more robust human literature.^{9,10} Documented efficacy is strongest for carbon monoxide (CO) toxicity and decompression sickness.¹¹⁻¹³ These are uncommonly encountered in veterinary medicine, but if a patient were presented with CO toxicity, HBOT might be effective in reducing CO half-life.¹⁴

Several laboratory studies in small animals exist, including one that incorporated an autogenous cancellous bone graft. This study in cats demonstrated that a median percentage of bone was marginally higher in the group that received HBOT as compared with those that did not receive treatment (58.23% vs 47.06%, respectively); on removal of a single outlier, these results were statistically significant.¹⁵ Another feline study that featured blinded observers compared skin flap viability in which the flap color appeared subjectively healthier in the treated groups.¹⁶

A study in canine cardiac arrest patients showed improved neurologic outcome in both neurologic deficit scoring and reduced neuronal death postarrest in dogs that received HBOT.¹⁷ Dogs have also been used as a model for the effects of HBOT on the CNS, with positive results reported in the HBOT-treated groups subjected to complete global cerebral ischemia,¹⁸ spinal cord compression,¹⁹ and ischemic spinal cord injury.²⁰

Anecdotal veterinary treatment applications in various species have involved crotalid envenomations, refractory osteomyelitis, reperfusion injury, myocardial ischemia, pancreatitis, and anaerobic infections.^{8,21,22} Results from a retrospective study of HBOT suggest that the following conditions were frequently treated: compressive and vascular myelopathies, crotalid envenomation, surgical or traumatic wounds, and atypical infections.²³ The reliance of HBOT practitioners on low-grade evidence has likely

prompted some to withhold advocacy for the treatment until additional information is made available by proponents.

Treatment Mechanics

A hyperbaric chamber requires substantial and reliable grounding to prevent static or other sparks that can pose a fire risk. An appropriate chamber must be purchased or leased, and oxygen must be delivered to a fixed chamber location. Patients should be supervised during the entire process, and prohibited materials (eg, synthetic bandages or fabrics, electronics, petroleum-based drugs or ointments) should be avoided, as they can be flammable or pose a static electricity spark risk.

Total treatment times vary among practitioners, but a standard time of approximately 1.25 hours (inclusive of a gradual pressurization and depressurization period) has been documented.²³ IV access and therapy may be difficult unless the chamber is equipped with a special ingress port. Use of sedatives with vasoconstrictive properties (eg, α_2 -agonists) should be avoided until additional information is available. Although many patients appear to relax during the session, chamber noise and confinement may be a source of anxiety for others. Treatments are often repeated and may be performed once or twice daily over several consecutive days, depending on the condition being treated and apparent patient response.

Complications & Contraindications

Oxygen toxicity is the foremost concern with HBOT, with a grand mal seizure being the primary sign in animals.²³ However, the incidence is likely low based on limited data at 2 ATA for 45 minutes,²³ and the risk is dose dependent.^{24,25} Intra-session seizures are managed with gradual decompression and monitoring. There are no reports of any epileptic predisposition following HBOT-induced seizures.

Barotrauma has not been reported in the veterinary literature, but the theoretical possibility is explained by Boyle's Law (see **Principles & Physiology**, page 37). Trauma to the tympanic membrane or lungs is a primary concern. Any potential for entrapment of air in critical structures, such as in pre-existing pulmonary bullae or pneumothorax, should be avoided, and patients with these conditions should likely not receive treatment. Other important considerations in veterinary patients include sedation (if necessary), minimizing static electricity, avoiding exposed metal implants, and constant monitoring by trained team members.²⁶

Recent HBOT-related deaths of a patient while in a small animal chamber and of both an attendant and a patient in an equine chamber explosion highlight the need for appropriate safety precautions.^{27,28} Training courses are provided by veterinary-specific chamber manufacturers and third-party hyperbaric technologist programs. Owners should be informed of the risks for oxygen toxicity and for barotrauma before each HBOT session.

CLINICAL POTENTIAL & LIMITATIONS

Despite a recent increase in interest and prevalence of veterinary HBOT, it remains a less accessible modality, with only a few options (if any) available in each state. Resources such as the Veterinary Hyperbaric Medicine Society (vhbot.org) and Hyperbaric Veterinary Medicine (hvmed.com) provide location maps of US veterinary clinics that have a chamber. Although cost varies by institution, the average cost of HBOT (based on treatment time and ongoing plan) is approximately between \$100 and \$200 per session. Because of the potential financial and geographic limitations, it is important to discuss the entire hyperbaric treatment plan with the client and set reasonable goals before initiating therapy or suggesting referral.

CONCLUSION

Because of its physiologic effects in other species, HBOT holds therapeutic promise in animals and deserves clinical and research attention. However, the therapy is not benign, and understanding the basics of HBOT and possible complications is critical. Because the clinical information, apart from expert opinion and research experiments with small numbers, remains minimal, research is essential to expand information about the physiology behind the modality, condition-specific treatment parameters, and appropriate and efficacious indications for use in veterinary patients. ■

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TRIFEXIS®
(spinosad + milbemycin oxime)
Chewable Tablets

Caution: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.
Before using TRIFEXIS chewable tablets, please consult the product insert, a summary of which follows:

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 infestations (*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.

Dosage and Administration:
TRIFEXIS is given orally, once a month at the minimum dosage of 13.5 mg/lb (30 mg/kg) spinosad and 0.2 mg/lb (0.5 mg/kg) milbemycin oxime body weight. For heartworm prevention, give once monthly for at least 3 months after exposure to mosquitoes (see EFFECTIVENESS).

Contraindications:
There are no known contraindications to the use of TRIFEXIS.

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, a component of TRIFEXIS (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 *D. 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 (see ADVERSE REACTIONS). 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 and 176 treated with an active control), no serious adverse reactions were attributed to administration of TRIFEXIS. All reactions were regarded as mild.

Over the 180-day study period, all observations of potential adverse reactions were recorded. Reactions that occurred at an incidence >1% (average monthly rate) within any of the 6 months of observation are presented in the following table. The most frequently reported adverse reaction in dogs in the TRIFEXIS group was vomiting.

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
Dermatitis	1.47	1.45
Skin Reddening	1.37	1.26
Decreased appetite	1.27	1.35
Pinna Reddening	1.18	0.87

*n=176 dogs

In the US field study, one dog administered TRIFEXIS experienced a single mild seizure 2 1/2 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 suspected adverse drug events, contact Elanco Animal Health at 1-888-545-5373. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or <http://www.fda.gov/AnimalVeterinary/SafetyHealth>

Post Approval Experience (Mar 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. Spinosad, a component of TRIFEXIS, kills fleas before they can lay eggs. If a severe environmental infestation exists, fleas may persist for a period of time after dose administration due to the emergence of adult fleas from pupae already in the environment. 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.

Palatability:

TRIFEXIS is a flavored chewable tablet. In a field study of client-owned dogs where 175 dogs were each offered TRIFEXIS once a month for 6 months, dogs voluntarily consumed 54% of the doses when offered (plain as if a treat, and 33% of the doses when offered in or on food. The remaining 13% of doses were administered like other tablet medications.

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