TOP 5

TOP 5 DERMATOLOGIC INDICATIONS FOR PENTOXIFYLLINE IN DOGS

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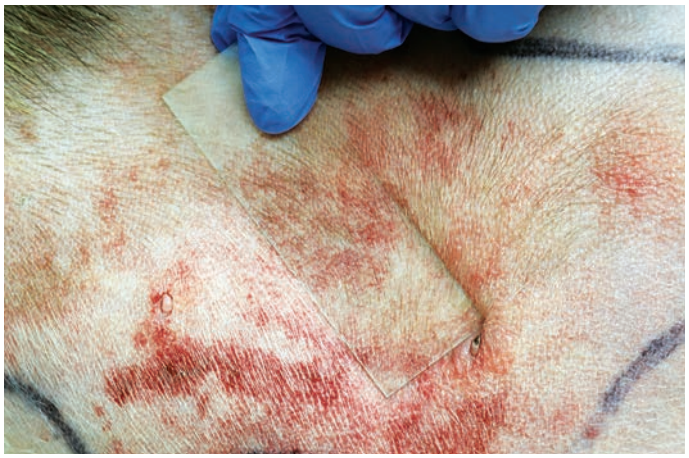
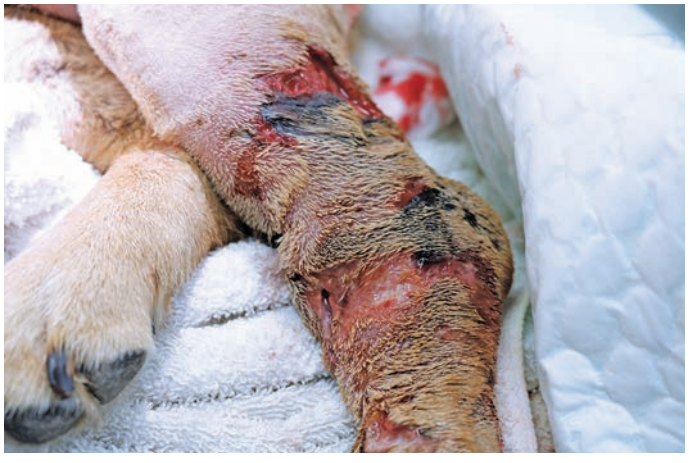
Pentoxifylline is a methylxanthine derivative that inhibits phosphodiesterase to raise intracellular cyclic adenosine monophosphate levels[1]; this can have many global effects, including improved circulation and reduced inflammation.[1] Pentoxifylline inhibits microvascular constriction and thrombus formation[1]; increases RBC and WBC deformability[1]; decreases proinflammatory cytokine production, neutrophil degranulation, natural killer cell activity, and leukocyte adhesion and adherence to keratinocytes[1-3]; increases leukocyte chemotaxis[1]; and stimulates fibroblasts to produce collagenase and promote wound healing.[1,2] Cytokines inhibited by pentoxifylline include tumor necrosis factor-α, interferon-γ, interleukin-1 (IL-1), IL-6, IL-8, and IL-10.[1]

TOP 5 DERMATOLOGIC INDICATIONS FOR PENTOXIFYLLINE

1. Cutaneous Vasculitis
2. Canine Familial Dermatomyositis
3. Other Ischemic Dermatopathies
4. Allergic Contact Dermatitis
5. Atopic Dermatitis



▲ **FIGURE 1** Multifocal to coalescing erythematous macules on the ventral abdomen of a dog with cutaneous vasculitis. Because the lesion does not blanch on diascopy, it is likely due to vasculitis or hemorrhage. *Image courtesy of Amelia White, Auburn University*



▲ **FIGURE 2** Full-thickness dermal necrosis on the hock of a patient with a neutrophilic necrotizing vasculitis suspected to be secondary to a spider bite. Pentoxifylline (25 mg/kg PO every 12 hours) and open wound management were provided. *Image courtesy of Karly Hicks, Auburn University*

Pentoxifylline (10-30 mg/kg PO every 8 to 12 hours) has a reported elimination half-life of 24 to 404 minutes that supports 8-hour administration.[4-6] In dogs, oral bioavailability is variable and reported to be 15% to 50%.[5,6] Pentoxifylline is available as a 400-mg extended-release tablet and is commonly halved or quartered to achieve the intended dosage.[5,6] No controlled studies have directly investigated the pharmacokinetic effects of breaking the extended-release tablet. Pentoxifylline is generally well-tolerated in dogs, and GI upset is the most commonly reported adverse effect.[5,6] Anecdotal reported use in veterinary medicine is vast; however, peer-reviewed studies evaluating its efficacy for the treatment of specific diseases are limited and generally retrospective. Based on anecdotal evidence in human and veterinary medicine, there is believed to be a lag in onset to clinical effect that may last several months.[6-8] Previously, concerns about cost limited the use of pentoxifylline in veterinary medicine, but affordable generic formulations are now available.

Following are 5 common uses of pentoxifylline in veterinary dermatology according to the authors.

1 Cutaneous Vasculitis

Cutaneous vasculitis refers to inflammation of the blood vessels in the skin (***Figure 1***) that results in altered blood flow and ischemic necrosis of the skin (***Figure 2***).[9] The condition may be idiopathic or caused by adverse drug reaction, infection, insect bite, or neoplasia.[8] Treatment should address the underlying cause and repair tissue damage.[9] Pentoxifylline is an ideal treatment (regardless of cause) because of its effect on perfusion and inflammation.

Because pentoxifylline has a potential delayed onset of effect, it is often combined with other drugs (eg, glucocorticoids).[9] In a retrospective study,[10] 9 of 19 dogs with vasculitis were treated with pentoxifylline (10-20 mg/kg PO every 12 hours) alone (1 dog) or in combination (8 dogs) with prednisone (1.5-3 mg/kg/day) with variable success. Six dogs had complete resolution, 2 had

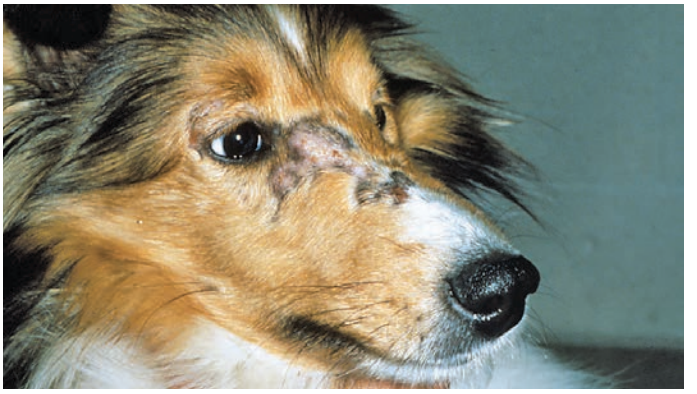
partial resolution, and 1 failed to respond. Of the 6 dogs with complete resolution, 3 relapsed when prednisone was tapered, suggesting that pentoxifylline may be insufficient when used alone to treat vasculitis.[10] Insufficient dosage and frequency could explain the limited success and lack of response in 3 dogs.[10] Despite reports of variable success, pentoxifylline is often used for the treatment of vasculitis.

2 Canine Familial Dermatomyositis

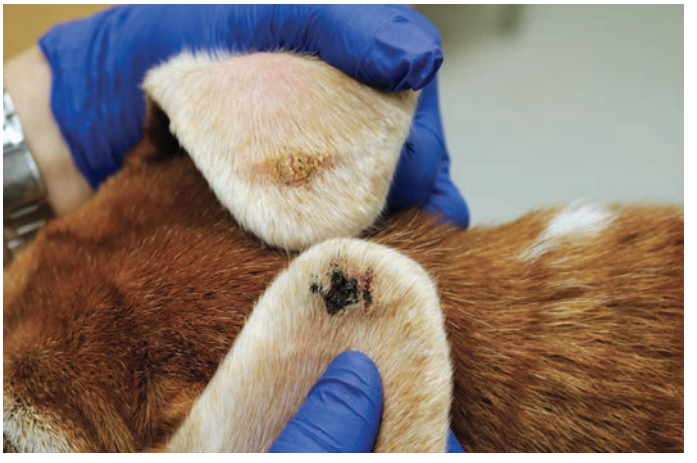
Canine familial dermatomyositis (CFD) is an inherited, ischemic disease of the skin, blood vessels, and muscle that predominantly affects Shetland sheepdogs and collies; however, other dog breeds can also be affected.[11] Lesions occur in the first few months of life and can vary from minor alopecia (***Figure 3***) to severe dermal ulceration and muscle atrophy. CFD is incurable; many treatments have been attempted with limited success. In a study, 10 dogs with CFD had partial or complete resolution of cutaneous lesions after receiving pentoxifylline (25 mg/kg PO every 12 hours for 12 weeks).[12] The median time to initial response was 6 weeks, supporting a lag in onset of effect.[12] No adverse effects, including clinicopathologic abnormalities, were observed, further supporting the relative safety of pentoxifylline as compared with other therapeutic options.[12]

3 Other Ischemic Dermatopathies

Ischemic dermatopathy refers to several clinical syndromes characterized by overall nutrient and oxygen deficiency in the skin,[13] including CFD, rabies-vaccine–induced vasculitis, vaccine-associated ischemic dermatopathy, familial cutaneous vasculopathy in German shepherd dogs, pinnal vasculitis (***Figure 4***), and idiopathic ischemic dermatopathy.[13] In a study, 3 dogs with rabies-vaccine–induced vasculitis had partial to complete hair regrowth 12 to 16 weeks after receiving pentoxifylline (15 mg/kg PO every 12 hours) combined with prednisone (0.8-3 mg/kg/day PO).[10] In a retrospective study of 177 dogs with ischemic dermatopathy, the majority of dogs (91.3%) were treated with either pentoxifylline alone or as adjunctive therapy, with a mean dosage of 47.12 mg/kg/day PO (range, 18-112.5 mg/kg/day PO).[13] Despite common use, no difference was found between dogs treated and dogs not treated with pentoxifylline. It was concluded that the retrospective nature of the study and variability in dosing regimens could explain this finding. Additional prospective, placebo-controlled studies are needed to determine the effectiveness of pentoxifylline in the treatment of ischemic dermatopathies. Despite limited evidence in the literature, the hemorrheologic properties of pentoxifylline could be favorable for the management of ischemic dermatopathies.



▲ **FIGURE 3** An alopecic, ischemic lesion on the bridge of the nose due to dermatomyositis



▲ **FIGURE 4** Bilaterally symmetric crusted lesions at the apex of the pinnae, consistent with pinnal vasculitis

CFD = canine familial dermatomyositis

4 Allergic Contact Dermatitis

Allergic contact dermatitis (ACD) is a type IV hypersensitivity reaction.[8,14] Reported causes of ACD in dogs include ingestion of plants, topical medications, detergents, cleansers, fibers, and plastic.[8,14] Pentoxifylline inhibits tumor necrosis factor-α, which is a critical mediator of ACD.[1,14] Pentoxifylline (10 mg/kg PO every 12 hours) was protective in preventing clinical signs in 3 dogs with known contact allergy to plants in the Commelinaceae family.[14] A clinical effect was observed within 2 days of onset of therapy and persisted for 7 days following discontinuation of therapy.[14] Treatment duration was limited to 3 to 5 weeks due to the cost of therapy.[14] Pentoxifylline has become less cost-prohibitive; thus, it can be a reasonable choice for prevention of clinical signs of ACD when avoidance is not possible. Major limitations of this study were the few number of dogs included and its retrospective nature. Additional investigations are required to determine the effectiveness of pentoxifylline in the treatment of ACD.

5 Atopic Dermatitis

Canine atopic dermatitis (CAD) is a common allergic dermatosis characterized by hypersensitivity to environmental allergens, primarily mediated by immunoglobulin E (IgE).[15] CAD can be challenging for the patient, pet owner, and clinician despite available pharmacologic management options. Although pentoxifylline is not considered a mainstay for management of CAD, limited research suggests it may have value as adjunctive therapy.[16,17] One study in normal dogs demonstrated that pentoxifylline inhibited late-phase inflammation by inhibiting IgE-mediated mast cell degranulation and eosinophil recruitment at the site's wheal formation.[18] These findings suggest pentoxifylline may have some effect in managing IgE-mediated inflammatory diseases. A double-blinded, placebo-controlled, crossover study of 10 atopic dogs showed that pentoxifylline (10 mg/kg PO every 12 hours) reduced pruritus scores by 50% in one-third of dogs over 4 weeks.[16] Dexamethasone and pentoxifylline have an in vitro synergistic effect on cytokine production via human leukocytes.[19] Pentoxifylline may have use as a steroid-sparing agent in dogs with CAD, but further studies are warranted to confirm its efficacy.[15,16]

In addition to these indications, anecdotal evidence suggests pentoxifylline may be useful for treatment of vesicular cutaneous lupus erythematosus, erythema multiforme, acral lick dermatitis, and metatarsal fistulae in German shepherd dogs.[8] Recent evidence evaluating the use of pentoxifylline in the treatment of dermal arteritis of the nasal philtrum and symmetric lupoid onychodystrophy suggests this drug may be an effective sole or adjunctive treatment in the management of these diseases.[20,21] Controlled clinical studies regarding the efficacy of pentoxifylline are lacking. Because of its relatively affordable cost and minimal adverse effects, pentoxifylline may be a useful adjunct therapeutic for dermatologic conditions in which improved microcirculation and reduced inflammation are desired.

ACD = allergic contact dermatitis
CAD = canine atopic dermatitis
IgE = immunoglobulin E

See page 24 for references.

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Many dogs are susceptible to developing dirty or infected ears. When they get an ear infection, this can complicate treatment. By recommending T8 Keto® Flush as treatment support, you can help keep your patients' ears healthy.

Common ear issues:

- **Presence of dirt and debris**
- **Too much moisture**
- **Waxy, crusty or gooey buildup**
- **Unpleasant odors**
- **Yeast or bacterial infections**

T8 Keto offers Tris-EDTA and ketoconazole in a patented alkaline, water-based formulation combined with mild surfactants for gentle cleansing and flushing of patients' ears. When infections strike, this bacteria-potentiating product raises the pH of the ear, priming it for other topical treatments.

Tris-EDTA to damage harmful bacteria

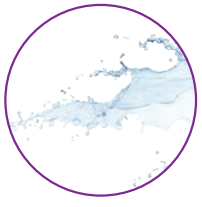
Ketoconazole for proven activity against fungus

Bacteria Potentiating Tris-EDTA

Tris-EDTA damages and destabilizes bacterial cell walls, especially gram-negatives. This, in turn, increases susceptibility of bacteria to antimicrobial therapies, particularly fluoroquinolones, aminoglycosides and silver sulfadiazine.[3,4]

Kills Microorganisms Fast

T8 Keto provides 60-second rapid kill of common ear pathogens such as *Malassezia pachydermatis* and *Pseudomonas aeruginosa* in *vitro*.*[1] It also has demonstrated in vitro activity against *Staphylococcus spp*, *Staphylococcus pseudintermedius*, *Proteus* and *B-hemolytic streptococcus*.*[2]



Non Irritating, pH- Appropriate Base

T8 Keto has an alkaline (pH 8.5) base. This helps maximize Tris-EDTA's activity. And because fluoroquinolones and aminoglycosides work better in an alkaline environment, it helps set your treatment protocol up for success.[5]

Ceruminolytic Activity

Common pathogens actively work against your treatment protocol by actively creating debris, wax and other discharge that act as a barrier. The cleaning action of T8 Keto flush breaks apart and removes:

- **Excessive wax and ceruminous discharge**
- **Inflammatory debris**
- **Biofilms and pus**

This allows topical medications to reach deep into the ear canal, including the horizontal canal where most of the infection typically resides.

T8 Keto promotes ear health and the normalization of the ear canal, including epithelial migration, which is key to restoring the cell layer that helps prevent the entry of pathogens and leakage of fluids.

Pseudomonas triggers a purulent, supportive discharge and is a potent biofilm producer.

Malassezia leads to excessive ceruminous production and wax buildup.

In addition, benzyl alcohol provides a number of benefits. It helps prevent product contamination after repeated use in infected ears. It also provides antiseptic activity against Gram-positive cocci and Gram-negative rods.[2]

This formula does not sting or burn, making it potentially more pleasant for the patient, aiding in compliance.

To learn more about adding T8 Keto to compliment your treatment regimen, contact your Elanco Sales Representative or Customer Service at (800) 633-3796.

*The clinical significance of in vitro data has not been determined.

1 Elanco Animal Health. Data on file.
2 Cole LK, Luu DH, Rajala-Schultz PJ, et al. Am J Vet Res. 2006; 67:1040-1044.
3 Farca AM, Piromalli G, Maffei F, et al. J Small Anim Pract. 1997; 38(6): 243-245.
4 Noxon J. In: Proceedings. Central Veterinary Conference. August 26-29, 2016. Kansas City, Missouri.
5 Bloom P. In Central Veterinary Conference Proceedings. 2017.

CAUTION: For topical use on dogs, cats and horses. Avoid contact with eyes. If eye contact occurs or skin irritation develops, rinse thoroughly with water, discontinue use and contact your veterinarian. Available through licensed veterinarians only.

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Contains Ketoconazole and Tris-EDTA

Kills common pathogens within one minute in vitro[1]

Call Customer Service at 1-800-633-3796 or contact your sales representative.

[1]Elanco Animal Health. Data on file. **Malassezia and Pseudomonas.*

CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian. For topical use on dogs, cats and horses. Avoid contact with eyes. If eye contact occurs or skin irritation develops, rinse thoroughly with water, discontinue use and contact your veterinarian.

WARNING: Keep out of reach of children. Not for human use.

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