



# Minocycline as Doxycycline Alternative

FROM THE DESK OF  
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## ISSUE

### “RECENT SHORTAGES OF DOXYCYCLINE HAVE LED TO PRICE INCREASES; I NEED AN ALTERNATIVE.”

Commercial suspensions of doxycycline are expensive and only stable for 2 weeks once reconstituted. Compounded doxycycline in aqueous vehicles is typically only stable for 7 days and is associated with a high risk for treatment failure from unstable product.<sup>1</sup>

## ANSWER

### CONSIDER MINOCYCLINE

Minocycline and doxycycline are semisynthetic antibiotics in the tetracycline family. Both are bacteriostatic; prevent bacterial growth by interfering with protein synthesis; and have antibacterial, anti-inflammatory, neuroprotective, cytoprotective,<sup>2,3</sup> antiprotozoal, and anthelmintic effects,<sup>4,5</sup> but there are important differences to consider.

### Lipophilicity & Tissue Distribution

Minocycline is strikingly more lipophilic (5x) than is doxycycline, allowing for a higher degree of intestinal absorption and tissue penetration.<sup>6</sup> As a result, minocycline concentrates in lipid-rich (eg, brain, adipose) tissue. Minocycline concentrations in canine brain tissue are reportedly 3x those of doxycycline<sup>6</sup>; although minocycline may be preferred for treating CNS infections, it may be associated with increased risk for CNS side effects, including vestibular disturbances.<sup>5</sup> Theoretically, dogs carrying the *MDR1* gene mutation (*ABCB1-1Δ*) may be more susceptible to CNS side effects caused by minocycline than by doxycycline, as both drugs are transported by P-glycoprotein and minocycline is more lipophilic than doxycycline; however, this has not been observed clinically.<sup>5,7</sup>

Minocycline and doxycycline readily penetrate the blood-ocular barrier; however, doxycycline concentrations in canine aqueous and vitreous humor are 2x those of minocycline,<sup>6</sup> so doxycycline may be preferred in dogs with ophthalmic infections. Both drugs distribute into the prostate, heart, lungs, pleural fluid, bronchial secretions, synovial fluid, bone, kidney, bile,

skin, thyroid, and saliva of dogs.<sup>6</sup> Because cats have a higher degree of plasma protein binding than do dogs, free drug concentration in interstitial fluids may be less than in dogs.<sup>8</sup>

### Metabolism & Elimination

Both doxycycline and minocycline are extensively metabolized in the liver and excreted in feces as inactive metabolites. In dogs, ≈75% of a doxycycline dose is eliminated in feces, with 16% to 22% eliminated in urine; ≈80% to 90% of a minocycline dose is eliminated in feces, with only 6% to 15% eliminated in urine.<sup>6</sup> Because of the low achievable urine concentrations of both drugs, they may not be ideal for treating UTIs. However, because of their lipophilic nature, both drugs demonstrate excellent penetration into prostatic fluid and tissues and may be useful in treating prostatitis. In addition, because of the low renal clearance of both drugs, dose adjustment is not necessary for either drug in patients with renal insufficiency.

Following absorption in dogs, both doxycycline and minocycline are passively diffused from serum into the lumen of the intestine, where they are chelated by metallic ions and other molecules causing drug inactivation.<sup>9</sup> Tetracyclines have a high affinity to form chelates with polyvalent metallic cations such as Fe<sup>+++</sup>, Fe<sup>++</sup>, Al<sup>+++</sup>, Mg<sup>++</sup>, and Ca<sup>++</sup>.<sup>9</sup> Many of these tetracycline-metal complexes are either insoluble or otherwise poorly absorbable from the GI tract.<sup>9</sup>

### Pharmacokinetics

Doxycycline and minocycline have variable GI absorption (28%-75%), which appears to be significantly reduced (20%-40%) when food is in the GI tract.<sup>10,11</sup> In dogs, doxycycline appears to be chelated by milk and polyvalent metallic cations to a greater extent than does minocycline.<sup>6</sup> Both drugs should be administered on an empty stomach, and meals containing high iron or calcium content should be avoided.<sup>10</sup> Because concurrent administration of sucralfate may significantly reduce oral absorption of both drugs (>2×), it should be given 2 hours after antibiotic administration.<sup>12</sup>

After absorption, the elimination half-lives of doxycycline and minocycline appear to be highly variable. In dogs, the half-life for doxycycline is ≈6.5 to 7.3 hours vs 4 to 7.3 hours for minocycline.<sup>11,13</sup> In cats, the half-life for doxycycline is 4.56 hours vs 6.3 hours for minocycline.<sup>8,14</sup> Doxycycline is highly protein-bound in dogs (82%) and cats (98%), whereas minocycline is slightly less protein-bound (dogs, 75%; cats, 46%-60%). Minocycline's lower

level of protein binding in dogs and cats permits higher concentrations of free unbound drug capable of distributing into interstitial fluid where bacterial infections often occur, which suggests better efficacy.

### Spectrum of Activity

Doxycycline and minocycline are frequently used to treat canine and feline infections caused by *Pasteurella* spp, *Borrelia* spp, *Bordetella* spp, *Chlamydia* spp, *Ehrlichia* spp, *Leptospira* spp, *Mycoplasma* spp, and *Rickettsia* spp.<sup>15</sup> However, both drugs can also cover gram-negative bacteria (eg, *Acinetobacter* spp, *Bartonella* spp, *Brucella* spp, *Campylobacter* spp, *Enterobacter* spp, *Escherichia coli*, *Francisella tularensis*, *Klebsiella* spp, *Yersinia* spp), gram-positive bacteria (eg, *Bacillus anthracis*, *Streptococcus* spp, *Staphylococcus* spp), anaerobes (eg, *Clostridium* spp, *Fusobacterium* spp), and others (eg, *Actinomyces* spp, *Nocardia* spp, *Wolbachia* spp).<sup>15</sup>

Because of minocycline's increased lipophilicity, its spectrum of activity is enhanced as compared with doxycycline. Its ability to penetrate intracellularly and cross physiologic barriers allows for higher tissue concentrations of the drug. Because minocycline can achieve concentrations in the CNS that are 3× higher than those achievable by doxycycline, minocycline is the drug of choice for treating susceptible CNS infections (eg, neuroborreliosis).

Although neither drug is the drug of choice for treating staphylococcal infections, both are useful in treating methicillin-resistant staphylococcal infections lacking the *tetK* resistance gene. Minocycline is considered the preferred drug for treating methicillin-resistant *S pseudintermedius* because it has better coverage in these methicillin-resistant organisms (65%) than does doxycycline (38%).<sup>11</sup> Furthermore, minocycline does not induce its own resistance as does doxycycline.<sup>16,17</sup> Minocycline has also shown efficacy against multidrug-resistant strains of *Acinetobacter baumannii* without the *tetB* gene and may be useful as monotherapy or in combination therapy when managing such cases, provided the infection is not a UTI.<sup>18</sup>

Both drugs are effective for adjunctive treatment of canine heartworm disease by reducing symbiotic populations of *Wolbachia* spp. Although doxycycline has been recommended, minocycline has shown superiority as an anti-*Wolbachia* spp treatment in human filariasis, warranting further study of its use in treating canine heartworm disease.<sup>4</sup>

## Anti-Inflammatory, Immunomodulatory, & Neuroprotective Effects

In humans, both drugs have shown to be effective anti-inflammatory agents in treating rheumatoid arthritis and osteoarthritis. Doxycycline has demonstrated superior anti-inflammatory effects in studies of rodents, but minocycline had radical scavenging activity 10× that of doxycycline.<sup>19</sup> Both drugs have demonstrated neuroprotective effects in animal models of cerebral ischemia, and both appear to reduce inflammatory responses to *Borrelia burgdorferi*.<sup>2</sup> In human medicine, minocycline has emerged as the most effective tetracycline regarding neuroprotection in experimental models of ischemia, traumatic brain injury, and neurodegenerative conditions<sup>20</sup>; if minocycline is administered to humans 6 to 24 hours after the onset of a stroke, outcome is improved vs placebo.<sup>21</sup> Although not yet studied in dogs and cats, minocycline may be preferred for treating CNS-related inflammatory conditions.

## Adverse Reactions

Both drugs share similar frequent side effects (eg, nausea, vomiting, diarrhea, anorexia). Use of doxycycline monohydrate reduces GI upset as compared with doxycycline hyclate. Both minocycline and doxycycline are salt bases that can irritate mucous membranes and cause esophagitis and esophageal strictures if administered to cats in capsule form.<sup>15</sup> Both may also cause permanent tooth discoloration in young animals and should not be administered to pregnant or lactating animals.<sup>15</sup> Black thyroid pigmentation and thyroid hyperplasia associated with prolonged minocycline ingestion was first described as an incidental finding in laboratory dogs.<sup>22</sup> Recent reports in the human literature suggest that black thyroid is linked to chronic minocycline ingestion<sup>22</sup>; to date, a single case was reported following a limited doxycycline course.<sup>23</sup> In humans, *black thyroid* is associated with a higher incidence of thyroid carcinoma as compared with the general population.<sup>24</sup> This collectively suggests that monitoring thyroid function with long-term veterinary therapy may be prudent.<sup>15</sup> Both drugs can cause hypotension and cardiovascular depression if administered via rapid IV administration.<sup>25</sup>

Although the incidence of adverse events for either drug has not been compared between drugs in animals, in humans many side effects are more common with minocycline.<sup>21</sup> Because of minocycline's increased CNS penetration, dizziness, vertigo, lightheadedness, and headaches are more frequent in humans

taking this drug.<sup>5</sup> Autoimmune drug-induced lupus, serum sickness, and elevated intracranial pressure appear to be more commonly reported in humans taking minocycline, whereas doxycycline reportedly has more GI and photosensitivity reactions.<sup>26</sup> Although an association between minocycline- and doxycycline-induced autoimmune disease has not been reported in dogs and cats, doxycycline may be the preferred drug for patients with pre-existing autoimmune diseases due to its lower reported incidence in humans.

## Dosing Protocol

The established doxycycline dosage in dogs is 5-10 mg/kg PO q12h and in cats is 5 mg/kg PO q12h or 10 mg/kg PO q24h, depending on the disease state.<sup>15,25</sup> Minocycline dose strategies are still being evaluated, but data to date suggest that doses similar to doxycycline are effective.<sup>11,14</sup> In dogs, doses of 5-10 mg/kg PO q12h appear to achieve sufficient concentrations for most organisms studied<sup>11,12</sup>; in cats, doses of 8.8 mg/kg PO q24h would provide appropriate concentrations for most bacteria, with minimum inhibitory concentrations of <0.5 µg/mL.<sup>14</sup>

## CONCLUSION

Doxycycline has historically been the drug of choice for many bacterial and protozoal infections in dogs and cats. Over the past few years, its availability has dwindled and costs have drastically increased. These changes, in addition to discontinuation of tetracycline, have forced veterinarians to find new alternatives. Minocycline may actually have advantages over doxycycline in some disease states. Because of its increased lipophilicity, minocycline has greater penetration into physiologic sites that are difficult to penetrate (eg, intracellular, abscesses, CNS), making it the preferred drug for infections in these sites.<sup>6</sup> Minocycline may also be preferred for treating methicillin-resistant *S pseudintermedius*.<sup>11</sup> Both drugs have similar side effects, although CNS ataxia and autoimmune side effects theoretically may be more prevalent with minocycline. Both drugs also have anti-inflammatory, immunomodulatory, neuroprotective, and anthelmintic effects, although minocycline potentially has slightly greater efficacy.<sup>2-5</sup> With similar dosing protocol and cost, minocycline can be an excellent substitute for doxycycline. ■

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## Chewable Tablets

**Brief Summary:** Please consult full package insert for more information.

**INDICATIONS:** Tri-Heart® Plus chewable tablets are indicated for use in prevention of canine heartworm caused by *Dirofilaria immitis* and for the treatment and control of ascarids (*Toxocara canis*, *Toxascaris leonina*) and hookworms (*Ancylostoma caninum*, *Uncinaria stenocephala*, *Ancylostoma braziliense*) in dogs and in puppies 6 weeks of age and older.

**PRECAUTIONS:** All dogs should be tested for existing heartworm infection before starting treatment with Tri-Heart® Plus chewable tablets. A mild hypersensitivity-type reaction, presumably due to dead or dying microfilariae and particularly involving a transient diarrhea has been observed in clinical trials with ivermectin alone after treatment of some dogs that have circulating microfilariae.

**Keep this and all drugs out of the reach of children.** In case of ingestion by humans, clients should be advised to contact a physician immediately. Physicians may contact a Poison Control Center for advice concerning cases of ingestion by humans.

**ADVERSE REACTIONS:** The following adverse reactions have been reported following the use of ivermectin at the recommended dose: depression/lethargy, vomiting, anorexia, diarrhea, mydriasis, ataxia, staggering, convulsions and hypersalivation.

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

**HOW SUPPLIED:** Tri-Heart® Plus chewable tablets are available in three dosage strengths for dogs of different weights. Each strength comes in convenient packs of 6 chewable tablets.

Store at controlled room temperature of 59–86° F (15–30° C). Protect product from light.

**For Technical Assistance, call Merck Animal Health: 1-800-224-5318**

Manufactured for: Intervet Inc. a subsidiary of Merck & Co. Inc., Summit, NJ 07901  
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