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Posaconazole treatment of refractory coccidioidomycosis in dogs

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Abstract

Background: The majority of dogs with coccidioidomycosis recover with administration of fluconazole or itraconazole, although some cases are refractory or the dogs do not tolerate administration of these medications.

Objectives: The objective was to describe the treatment outcomes and therapeutic monitoring of 8 dogs with refractory coccidioidomycosis treated with posaconazole.

Animals: Eight dogs with refractory coccidioidomycosis.

Methods: Retrospective case series. Medical records from Veterinary Specialty Center of Tucson were searched to identify dogs with refractory coccidioidomycosis that were treated with posaconazole. Clinical information and the results of monitoring trough serum posaconazole concentrations were retrieved.

Results: Eight dogs with refractory coccidioidomycosis were treated with 2.5 to 10 mg/kg per day of posaconazole. Six of 8 dogs recovered or developed clinical remission while administered posaconazole. Thirteen serum concentrations from 8 dogs tested were >1 μg/mL (range, 1.52 to >6 μg/mL) and the drug was well-tolerated by 7 dogs. One dog required dosage reductions and treatment was ultimately discontinued because of hepatotoxicosis.

Conclusions and Clinical Importance: Posaconazole should be considered as a treatment option for dogs with refractory coccidioidomycosis. Monitoring of indicators of liver function or injury along with therapeutic drug monitoring is recommended to tailor dosage in the event of hepatic toxicosis.

KEYWORDS
coccidioides, fungal infection, refractory, therapeutic drug monitoring

1 | INTRODUCTION

The dimorphic soil fungal pathogens, *Coccidioides posadasii* and *Coccidioides immitis*, cause both pulmonary and disseminated coccidioidomycosis in dogs. The most common presentation is fungal pneumonia,[1] though approximately 25% of dogs develop disseminated disease in a wide variety of other sites, ranging from bone to brain.[2,3] Both pulmonary and disseminated coccidioidomycosis are

Abbreviations: AGID, agar gel immunodiffusion; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CT, computed tomography; MIC, mean inhibitory concentration; UPLC/MS, ultraperformance liquid chromatography/mass spectrometry.

treated routinely with fluconazole and itraconazole administered for approximately 6 to 18 months.[1,4] In both respiratory and disseminated forms, a small proportion of cases are refractory, defined as failure to respond to administration of at least 2 first line treatments.[5] These cases require utilization of medications that can include amphotericin B, which is administered IV and is potentially nephrotoxic, and newer azoles with greater efficacy against fungal pathogens.[6,7]

Posaconazole is 1 such newer azole that can potentially be used to treat refractory coccidioidomycosis in dogs. It is a second generation triazole antifungal medication that has broad-spectrum activity against invasive fungal pathogens, including *Coccidioides* spp., that are refractory to treatment with other azoles and amphotericin B.[8-10] Posaconazole has a mean inhibitory concentration (MIC) against *Coccidioides* strains of 0.5 to 0.1 μg/mL in vitro,[11,12] and, in contrast to itraconazole, achieved a high rate of undetectable fungal burdens in treatment studies of mice infected with *Coccidioides* spp.[11,13]

Posaconazole is used to successfully treat refractory coccidioidomycosis in humans[5,6,14] and refractory aspergillosis in dogs,[15,16] but studies reporting the use of posaconazole in refractory coccidioidomycosis in dogs are lacking. Given the potential utility of posaconazole for treatment of refractory coccidioidomycosis, the goal of the current study was to describe a series of canine coccidioidomycosis cases treated with posaconazole. A secondary aim was to describe the usefulness of therapeutic drug monitoring when using posaconazole in dogs.

2 | MATERIALS AND METHODS

2.1 | Record review and criteria for selection of cases

This study was a retrospective case series undertaken via review of medical records from a single specialty referral veterinary hospital. The hospital database of Veterinary Specialty Center of Tucson was searched for dogs that received posaconazole for treatment of refractory coccidioidomycosis from 2011 through 2018. To be defined as a refractory case, dogs had to have coccidioidomycosis as defined by positive serology plus supportive imaging, clinical, and clinicopathological findings, or cytological or cultural proof of infection. In addition, the dogs must have failed to respond to at least 2 other antifungal medications. The history of diagnostics and treatment leading up to the institution of posaconazole were reviewed. Posaconazole doses, duration of treatment, and serum liver enzyme activities were extracted from the records. Response to treatment and survival status at manuscript preparation was recorded.

2.2 | Posaconazole monitoring

Timing, frequency, testing method and test results of therapeutic posaconazole concentration monitoring were reviewed. To measure trough posaconazole concentrations, sera were collected within 1 hour before the next scheduled dose of posaconazole and submitted to either the Fungus Testing Laboratory (University of Texas Health Sciences Center, San Antonio), which utilizes ultraperformance liquid chromatography/mass spectrometry (UPLC/MS), or the Infectious Diseases Research Laboratory, California Institute for Medical Research (San Jose, California), which uses a bioassay.[17] Tolerance to posaconazole was assessed based on clinical signs in the dogs and monitoring of serum chemistry variables.

3 | RESULTS

3.1 | Signalment and diagnosis

Eight dogs that received posaconazole for refractory coccidioidomycosis were identified. Dogs ranged in age from 1 to 11 years. The dogs included 4 mixed breed dogs and 4 purebred dogs represented only once. Six dogs were spayed females, and 1 dog was a castrated male. One female dog was intact at the time of initial evaluation but was spayed while being treated for coccidioidomycosis. Dogs were diagnosed with coccidioidomycosis based on combinations of history and clinical signs, serology via agar gel immunodiffusion assay (AGID), and diagnostic imaging findings consistent with the disease. All but 1 of the dogs had been diagnosed with coccidioidomycosis before seeking care at the referral hospital (range, 1-9 months), and all failed to respond to administration of at least 2 other antifungal drugs before initiation of treatment with posaconazole.

3.2 | Clinical and diagnostic findings of refractory coccidioidomycosis

All 8 dogs had pulmonary infiltrates and tracheobronchial lymphadenopathy, and 2 dogs also had disseminated disease characterized by osteomyelitis and peripheral lymph node enlargement. The prior antifungal treatments and key indicators of refractory coccidioidomycosis are shown in Table S1.

Clinical pathology changes that were present in the dogs at the time of initial evaluation included increased white blood cell count, characterized by neutrophilia (6 dogs; median 18 822 cells/μL; range, 13 981-23 325 cells/μL) and monocytosis (6 dogs; median 1964 cells/μL; range, 1539-3934 cells/μL), hyperglobulinemia (5 dogs; median 4.4 mg/dL; range, 4.1-8.4 mg/dL)), and hypoalbuminemia (4 dogs; median 2.1 mg/dL; range, 1.5-2.5 mg/dL). Serum anticoccidioidal AGID antibody titers at initial evaluation ranged from negative to ≥1 : 256 (median 1 : 32). One dog's titer increased from 1 : 32 to ≥1 : 256 during treatment with other antifungals. The 1 dog which was seronegative had spherules observed cytologically from aspiration of a lung lesion.

All 8 dogs had thoracic radiographs performed and 2 dogs had radiographs of affected limbs or axial skeleton as well. Common thoracic radiographic abnormalities in all dogs were regional to diffuse bronchointerstitial infiltrates and moderate to severe tracheobronchial lymphadenopathy. Other abnormalities included lobar alveolar infiltrates or lobar consolidation (2 dogs); nodules (5 dogs); mild pleural

effusion (2 dogs); sternal lymphadenopathy (2 dogs); and multiple cavitary lesions (1 dog).

Radiographic abnormalities of the limbs were detected in 2 dogs. One dog had lytic-proliferative lesions in multiple long bones, joint effusion in the stifle, carpal and tarsal joints, and erosive arthritis in the carpal and tarsal joints. One dog had lesions in the proximal and distal humerus bilaterally; this dog also had multiple cervical vertebral lesions detected by computed tomography (CT) that are detailed below.

Five of 8 dogs had CT of the thorax performed at least once and 3 dogs had repeat CT. Abnormalities identified on thoracic CT included tracheobronchial lymphadenopathy causing compression of the trachea and mainstem bronchi (5 dogs); nodules (5 dogs); bronchointerstitial infiltrates (5 dogs); consolidation of lung lobes (2 dogs); and multiple cavitary lesions (1 dog). One dog had CT of the cervical spine twice, revealing a lytic lesion of C2 and severe cervical lymphadenopathy on the initial evaluation, and additional lytic lesions of C3-C5 on the follow-up CT with no resolution of the earlier findings.

Other diagnostic test results included: bronchial washes revealing pyogranulomatous inflammation (3 dogs); ophthalmologic examination revealing anterior uveitis (2 dogs); aspirate cytology of consolidated lung or nodular pulmonary lesions revealing pyogranulomatous inflammation and spherules (2 dogs) or pyogranulomatous inflammation only (1 dog); culture of peripheral lymph nodes positive for growth of *C. posadasii* confirmed by PCR (1 dog); and synovial culture and cytology with nondegenerate neutrophils and no etiologic agents identified (1 dog).

3.3 | Drug treatment history before posaconazole

All dogs did not have sustained improvement of the coccidioidal disease or developed drug intolerance to fluconazole (generic; 8-10 mg/kg q12 h) and subsequently itraconazole (generic capsules or commercial oral solution) (3.2-7.7 mg/kg daily). Of 4 dogs treated with voriconazole (generic) (4-5 mg/kg q12 h) before starting posaconazole treatment, 1 was treated for <4 weeks and discontinued for unknown reasons, and 3 were discontinued for intolerance (2 hepatotoxicosis, 1 central nervous system adverse effects) after treatment periods ≤2 months. Additionally, 6 dogs also received amphotericin B lipid complex (range, 6-15 infusions of 0.5-0.2 mg/kg), with 3 dogs receiving more than 1 series of infusions 2 to 12 months apart. Treatment was stopped after 7 infusions in 2 of the dogs because of renal toxicosis (1 dog) and trembling, lethargy, nausea, inappetence, and weight loss after treatment (1 dog).

3.4 | Posaconazole treatment and monitoring

Seven of 8 dogs were treated with tablets or capsules at an initial dose of approximately 5 mg/kg/day (range, 4.7-5.5) either divided q12 h (n = 3) or q24 h (n = 4). The remaining dog was treated with posaconazole suspension (40 mg/mL) at a dose of 10 mg/kg once daily.

Posaconazole serum concentrations were measured approximately 4 weeks after beginning posaconazole treatment or approximately 2 weeks after dosage adjustment. Serum concentrations were measured by UPLC/MS for 7 dogs and bioassay for 1 dog. Posaconazole treatment doses, duration of treatment and serum concentrations are summarized in Table S1. All dogs demonstrated serum posaconazole concentrations >1 μg/mL (median 3.55 μg/mL; range, 1.52-4.89), which is considered to be in the therapeutic range for coccidioidomycosis based on in vitro and murine data.[11] Some of the dogs had concentrations considerably higher than 1 μg/mL. One dog's posaconazole dose was lowered to 3 mg/kg/day after 3 months because of a strong clinical response and serum concentration of 3.8 μg/mL with the initial dose of 5.5 mg/kg/day; the posaconazole concentration was not tested again after the dose reduction. One dog which had a very high serum concentrations (4.89 μg/mL) on the starting dose of 5.5 mg/kg/day underwent multiple dose reductions down to 2.5 mg/kg/day and serum concentrations remained above 1 μg/mL. The dog was clinically tolerating the medication but increasing serum activity of liver transaminases (ALT, AST), alkaline phosphatase (ALP), and concentration of bile acids triggered dose reductions with monitoring of serum drug concentration.

3.5 | Tolerability of posaconazole

Among the 8 dogs, 1 dog had decreased appetite while initially taking posaconazole; inappetance was successfully managed with use of capromorelin (1.25 mg/kg q24 h as needed) for 2 months until the dog's coccidioidomycosis improved. This dog also had other underlying conditions, including arthritis, lumbosacral disk disease, and chronic kidney disease. No observable adverse effects were noted by owners of the other 7 dogs.

The primary laboratory abnormalities noted in the dogs in this study were mild (<3-fold) to moderate (3- to 10-fold) increases in serum liver enzyme activities above reference ranges.[18] Seven of the 8 dogs were concurrently receiving glucocorticoids (prednisone, 0.25-0.5 mg/kg q24 h) when the serum chemistries were assessed 4 weeks after starting posaconazole and 5 of 8 dogs had mild to moderate increases in ALP, likely because of glucocorticoid induction. Mildly increased ALT was common, though the most concerning was a ≥3-fold increase in 2 dogs. The first of these dog's ALT values reduced over time and normalized with discontinuation of the prednisone and no adjustment in the dose of posaconazole. The other dog, which had a history of hepatic intolerance to both high dose fluconazole (10 mg/kg q12 h) and to voriconazole (4.6 mg/kg q12 h), demonstrated stable, mildly increased ALT serum activity (<200 IU/L) for 9 months on 2.5 mg/kg of posaconazole per day. Then an ALT of 566 IU/L was detected, which increased to 955 IU/L over a 2-month period and biopsy revealed reactive hepatitis. Though the dog still had multiple sites of radiographically unresolved osteomyelitis and an antibody titer of 1 : 16, clinical signs (lameness, pain, peripheral lymphadenopathy, weight loss, and tarsal, carpal and left stifle joint effusion) were largely resolved and posaconazole was discontinued. Serum liver enzyme activity returned to normal, and after

a 5-week hiatus from antifungal therapy, fluconazole (5 mg/kg q12 h) was restarted and serum liver enzyme activity remained within normal limits.

3.6 | Treatment outcomes

All dogs had clinical improvement initially. Median treatment time was 18 months (range, 14-19). Six dogs had resolution or remission of disease, and 5 dogs remain alive at the time of writing (Table S1). Of the 5 dogs still alive, 4 are in clinical remission with resolution of clinical, radiographic, and clinicopathologic abnormalities, and antibody titers ranging from <1 : 2 to 1 : 4. One is receiving no antifungal medication, 2 are receiving 5 mg/kg once daily of fluconazole, and 1 is administered a 2.8 mg/kg every other day dose of posaconazole because of owner reluctance to stop treatment even though there is radiographic resolution of disease. The fifth surviving dog had resolution of lung lesions and clinical signs with a reduction in antibody titer from ≥1 : 256 to 1 : 16, but has unresolved lesions in multiple bones that differ minimally from those on the initial radiographs. Posaconazole was discontinued after 17 months because of biochemical evidence of hepatotoxicosis and fluconazole was restarted (5 mg/kg q24 h). In the subsequent year on fluconazole, the titer decreased to 1 : 4 and the dog remains in clinical remission. A sixth dog with resolution of disease, including negative serology, was euthanized for unrelated health issues 4 months after the end of posaconazole treatment.

Two dogs were euthanized after 18 and 21 months of treatment. Both dogs had initial improvement in clinical signs after institution of posaconazole treatment. The pain from cervical and humeral osteomyelitis progressively worsened in 1 dog toward the end, and the other developed pneumothorax, presumptively from rupture of 1 of the cavitary lung lesions.[19]

4 | DISCUSSION

Posaconazole was efficacious in improving clinical signs in all 8 dogs with refractory coccidioidomycosis and resulted in clinical remission or resolution in 6 of 8 dogs. Whereas biochemical evidence of hepatotoxicosis was detected in 1 dog, and 1 dog developed temporary inappetence at initiation of therapy, posaconazole was well-tolerated. Therapeutic drug monitoring was useful in tailoring dosages of posaconazole.

The observations in this small case series are in line with human studies. In a small phase III clinical trial in humans with refractory coccidioidomycosis, posaconazole was efficacious in 5 of 6 patients that had failed other therapy, and in another study 75% of 16 patients improved with posaconazole therapy.[5,6] The median duration of administration of posaconazole was 18 months for the dogs in this study in which disease resolved, and that is similar to the duration of treatment reported in the human studies referenced above. The proportion of dogs and humans with refractory coccidioidomycosis that have clinical improvement from posaconazole is similar.

Posaconazole treatment is reported in dogs with disseminated and nasal aspergillosis,[15,16] disseminated *Chrysosporium*,[20] and disseminated *Westerdykella* infection,[21] infectious agents frequently refractory to other antifungal drugs. The dogs with disseminated infections of all 3 fungal agents ultimately died because of the disease after some period of improvement, with the exception of 2 out of 10 dogs which had long term remissions of disseminated aspergillosis.[15] Six of 8 dogs in the current case series of refractory coccidioidomycosis had resolved or improved disease, whereas 1 dog with disseminated disease and 1 dog with disease limited to lungs and thoracic cavity ultimately died despite treatment. These observations suggest that posaconazole is a reasonable treatment choice for dogs with refractory coccidioidomycosis.

The reports in the literature of dogs treated with posaconazole generally lack measurement of serum drug concentrations. Posaconazole is lipophilic and poorly soluble, and the commercial suspension has low bioavailability in humans, requiring daily doses of 800 mg to achieve therapeutic blood drug concentrations (~0.5-1 μg/mL).[22-24] Posaconazole delayed release (DR) tablets have greatly improved bioavailability for humans,[21] and bioavailability and half-life appear to be similarly greater in dogs receiving DR tablets compared to the commercial suspension.[23] Two German shepherd dogs with disseminated aspergillosis receiving posaconazole suspension 5 mg/kg q12 h had serum concentrations over 3 μg/mL, though the time of collection relative to drug administration was not reported.[15] In that study, 1 of the dogs responded and 1 did not respond to treatment. In this study of refractory coccidioidomycosis, the dogs had trough measurements of serum posaconazole at least once during treatment, and the dosing was successful in generating a posaconazole concentration above 1 μg/mL in all of them, regardless of the formulation of the posaconazole. However, similar to the 2 dogs in the aspergillosis study, achieving potentially therapeutic serum drug concentrations was not sufficient to resolve disease for all dogs in the cases reviewed. It is likely the failure to respond is related to a complexity of host and pathogen factors.

For 1 dog in this study, the therapeutic drug monitoring proved clinically important to managing toxicosis and continuing treatment in a dog that had no antifungal options left except posaconazole. The dosage reductions with repeated measurement of posaconazole concentrations helped manage hepatotoxicosis and allowed the dog to be treated for several months with continued clinical improvement before progressive hepatotoxicosis required discontinuation of the drug. By that time, the clinical signs, peripheral lymphadenopathy, and pulmonary radiographic abnormalities were resolved, though the bone lesions remained unchanged.

For 6 of the remaining dogs, serum concentrations were between 1 and 4 μg/mL, and the dose was not decreased because the drug was well-tolerated. However, the cost of posaconazole is high (~10 times generic fluconazole or itraconazole for same size dog) and it is possible that it could be used at lower doses with similar efficacy to reduce both costs of treatment and the potential for adverse effects. One dog in this cohort had the dose reduced by 45% without further drug serum concentration monitoring and successfully recovered. A single-dose pharmacokinetic study of DR tablets in dogs calculated that the

half-life is 42 hours and may allow for every other day dosing.[25] Treatment regimens less than daily should be evaluated with both clinical responses and therapeutic drug monitoring.

Adverse effects and hepatotoxicosis are frequent problems with azole antifungal administration.[1,26-28] Overall tolerability of posaconazole in both dogs and humans is reported to be good with almost no patients stopping treatment because of adverse effects.[15,16,29] In 166 human patients administered posaconazole, serum abnormalities in liver enzyme activities were infrequent, and the dose of posaconazole was not correlated with the increases except when other drugs with the potential to cause hepatotoxicosis were administered.[29] In that study, only serum liver activity test results between 5 and 14 days after starting the posaconazole were reported, whereas the dogs in the current study were tested at least 28 days after start of treatment, with periodic evaluation of serum chemistries throughout the months-long treatment period. With 1 exception, the dogs had transient increases, or they were mild (<3-fold increased ALT), considered clinically irrelevant, and did not further increase during treatment. Posaconazole was generally well-tolerated in these dogs over long treatment periods, but the discontinuation of posaconazole because of hepatocellular toxicosis in 1 dog indicates that dogs need to be monitored for hepatotoxicosis, as is recommended in humans.[30]

A limitation of this study is the retrospective nature of case reviews and the fact that it is an observational case series without a treatment control group or randomization. However, the apparent efficacy of posaconazole for refractory coccidioidomycosis in dogs is novel and the information should be helpful to practitioners treating severe fungal infections that are susceptible to posaconazole. The use of posaconazole in dogs is off-label, but all antifungal drug treatment in animals requires off-label use of drugs with the exception of the veterinary formulation of itraconazole solution, labeled for cats with ringworm (https://vetlabel.com/lib/vet/meds/itrafungol-1/).[31] It is possible that lower doses or different dosing schedules could also be efficacious, but this would require a prospectively designed study to investigate systematically. Finally, there was no control over the sourcing of the posaconazole in this retrospective review and serum concentrations might be affected by the formulation used.

Despite these limitations, this study shows that posaconazole can be effective in treating refractory coccidioidomycosis in dogs and that therapeutic drug monitoring is a useful tool to minimize the potential for toxicosis while assuring clinically relevant concentrations are present in serum.

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CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

All antifungal drugs administered to dogs reported in the manuscript constitutes off-label use of the drugs in animals in the USA.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Authors declare no IACUC or other approval was needed.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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