Selected systemic anti-fungal treatments for companion animals: Part 2
Systemic treatment of *Malassezia* dermatitis in dogs

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Malassezia dermatitis is still an under-diagnosed and under treated cause of pruritus especially in dogs. Keith Hnilica says in Small Animal Dermatology (3rd Edition) "Yeast dermatitis is currently the most commonly missed diagnosis in U.S. general practices. Any patient with leathery elephant skin-like lesions on the ventrum should be suspected of having *Malassezia* dermatitis." The problem is that in the early stages of *Malassezia* dermatitis, before the leathery elephant skin-like lesions develop, the presentation of *Malassezia* dermatitis mimics allergy and superficial pyoderma, and indeed, is often either secondary to hypersensitivity or at least concurrent with both, appearing as moderate to severe pruritus with erythema. That is why every pruritic animal needs to have cytology performed. However, as Hnilica says "Cutaneous cytology is not always successful for finding *Malassezia* organisms, requiring the clinician to rely on clinical lesion patterns to make a tentative diagnosis" and following on from that, to use response to therapy as part of the diagnostic approach.

In that vein, in an evidence-based review of treatments for *Malassezia* dermatitis in dogs in 2009, Negre *et al.* noted that the "diagnostic criteria for *Malassezia* dermatitis in dogs are still not clearly defined. It has been proposed that the diagnosis can be established when a dog with an abnormally high population of *M. pachydermatis* on lesional skin shows a good clinical and cytological response to appropriate antifungal treatment." So, we need a reliable treatment both to diagnose and to treat *Malassezia* infection in dogs.

In 1991 Mason and Evans reported on a dermatitis caused by *Malassezia* in 11 dogs. They reported that oral ketoconazole gave a good resolution of the dermatitis. Since that paper, ketaconazole has been the most commonly used medication to treat cases of *Malassezia* dermatitis. The dose rate varied from 5 to 10 mg/kg once or twice daily, but most dermatologists found that once daily treatment at the lower dose rate was sufficient. In 2008, Mayer *et al.* reported on the adverse effects of ketoconazole in dogs. They found that adverse effects occurred in 14.6% of the 632 treated dogs. These adverse incidents included vomiting (7.1%) anorexia (4.9%), lethargy (1.9%), diarrhoea (1.1%), pruritus (0.6%), erythema (0.3%) and other (2.5%). Increased liver enzyme levels were reported rarely. Anecdotally I have not uncommonly recognized the side effects of nausea and vomiting, although they usually respond to dose reduction and dosing with food.

Medscape reported that oral ketoconazole was discontinued in New Zealand on 1 December 2013 mainly due to concerns over the risk of hepatotoxicity in people especially when it was taken for prolonged periods. Other side effects in people were nausea and vomiting, constipation, headache, dizziness, abnormal liver function tests (15%) with severe hepatitis occurring in 1:10,000 patients. It was rarely fatal. Adrenal insufficiency and allergic skin rash including urticaria were also reported. This discontinuation means that ketaconazole is no longer available for canine treatment except as a compounded medication. What do we use instead?

In 2009 the evidence-based review mentioned previously, Negre *et al.* found that of the oral medications, there was fair evidence supporting the use of ketaconazole and itraconazole to treat *Malassezia* dermatitis. Itraconazole was compared to ketaconazole in two trials. There were no significant differences in any results between itraconazole pulse therapy and the daily administration of ketaconazole. Another study reported no significant difference between daily and pulse administration of itraconazole. The therapeutic doses were variable: 5 mg/kg once or twice daily for 3 to 4 weeks, or if pulsed, given on two consecutive days each week. Muller & Kirk's Small Animal Dermatology (7th edition) states that itraconazole has better tissue penetration and a longer half-life than ketaconazole, thus making it suitable for pulse dosing. The bioavailability increases when it is given with food. According to Muller & Kirk's, oral itraconazole takes 14 to 21 days to reach a steady state. It persists in skin for 2 to 4 weeks after treatment is discontinued. The four studies discussed in the evidence-based review of *Malassezia* interventions found that side effects were rare (4 of 49 cases); they were mainly vomiting and decreased appetite. Itraconazole is metabolized by the liver.

Fluconazole, another azole anti-fungal, wasn't discussed in the 2009 evidence-based review. Interestingly, an open, randomised, comparative study of oral fluconazole, itraconazole and terbinafine therapy in human onychomycosis (organism unspecified) found that terbinafine clinically cured 81% of cases, itraconazole cured 78%, and fluconazole cured 37%. This puts fluconazole in rather a poor light. However, the fluconazole was dosed once weekly, while the itraconazole was dosed twice daily for one week per month and the terbinafine was given once daily.

A noninferiority study in 2010 compared fluconazole and ketaconazole in combination with cephalexin in the treatment of dogs with *Malassezia* dermatitis. This study was designed as a double-blinded noninferiority trial to compare the clinical efficacy of fluconazole to that of ketaconazole, a known effective treatment. As the 25 dogs in the study had both yeast and bacterial dermatitis, concurrent treatment with cephalexin was used. The outcome of the antifungal therapy was assessed by comparing the number of *Malassezia* organisms seen on cytology, the presence of clinical lesions typical of yeast dermatitis, and an estimate

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of the dog's degree of pruritus before and after treatment. Both ketaconazole and fluconazole were dosed at 5–10 mg/kg PO once daily with food for three weeks. Clinical resolution of the *Malassezia* dermatitis was obtained in 77% of dogs in the fluconazole group (10 of 13 dogs) as opposed to 83% of the ketaconazole group (10 of 12 dogs). The pruritus was reduced by more than 50% in 85% of the fluconazole group and 83% of the ketaconazole group. In the fluconazole group, the mean reduction in pruritus was 62.6 % while it was 64.3% in the ketaconazole. The yeast count in the ketaconazole group was reduced by 97.8%; the fluconazole group by 95.9%. It is worth noting that mild adverse effects (mild and transient that did not require cessation of therapy) were seen in 46% of the fluconazole group and 50% of the ketaconazole group. It is very likely that some of the adverse effects were due to the cephalexin rather than the antifungals. These results indicate fluconazole is not inferior to ketoconazole for the treatment of *Malassezia* dermatitis in dogs.

Fluconazole is excreted largely unchanged through the kidneys. Because fluconazole has high bioavailability (>90%), a low incidence of side effects and renal excretion, it is a good choice in dogs with hepatic pathology. Obviously in dogs with renal impairment it should be avoided. It is normally dosed at 5 mg/kg once daily with or without food. Anecdotally some dogs respond better to fluconazole used at 10 mg/kg once daily.

Another systemic treatment for *Malassezia* dermatitis in dogs that was considered in the evidence-based review was terbinafine, an allymine. Because it minimally inhibits the P450 enzyme system, it has fewer drug interactions compared to ketaconazole and the other azoles. The efficacy of terbinafine was assessed in two trials, neither of which were particularly strong, with one having inadequate intention to treat analysis and one lacking blinding and randomisation. In the blinded, randomised study terbinafine was used for 3 weeks, at 30 mg/kg once daily (plus cephalexin twice daily) while ketaconazole was used at 5–10 mg/kg twice daily (plus cephalexin). A third group was given cephalexin only. The mean yeast count improved in all groups: 86.8% in the terbinafine group, 80.2% in the ketaconazole, and 28.8% in the cephalexin-only group. (Compare this with the higher quality fluconazole noninferiority study: 96% reduction for fluconazole and 98% for ketaconazole.) Both the ketaconazole+cephalexin and cephalexin-only groups gave better improvements in the clinical index score than the terbinafine+cephalexin group. However, the pruritus scores as judged by the owners were best in the terbinafine+cephalexin group (both the average total reduction of pruritus and the number of dogs improving more than 50%). Cytologically and clinically, *Malassezia* and bacterial skin infections resolved completely in only three of the dogs in all three groups. The evidence-based review reported this result as "an insufficient remission of clinical signs with only partial mycological improvement." However this applied equally to all three groups: the ketaconazole group as well as the other two, and ketaconazole is considered the gold standard of treatment.

The second study used terbinafine at 2.5 mg/kg once daily (1/10 of the standard dose rate of 30 mg/kg once daily) plus 1% terbinafine cream and a 2.5% selenium sulphide shampoo. Although clinical improvement was complete, the length of treatment was twice that of ketaconazole. The reviewers felt that there was insufficient evidence for recommending oral terbinafine. I would be cautious accepting that stricture as neither study was very powerful, and the second study in particular didn't use the recommended canine oral dose.

Based on the published data, and of course background anecdotal rumour, for the treatment of *Malassezia* dermatitis, I would replace ketaconazole with fluconazole used at 5 mg/kg once daily. Fluconazole is available in 50 mg, 150 mg and 200 mg capsules. If the yeast count and/or pruritus were not improved, I would consider switching to itraconazole at 5 mg/kg once daily with food either pulsed two consecutive days out of seven for three weeks or once daily for three weeks. Itraconazole is only available as a 100 mg capsule. Terbinafine at 30 mg/kg once daily with food could be considered if there were side effects with the azoles or potential drug interactions, as when avermectins are being used concurrently to treat Demodex. It is available as a 250 mg tablet which allows easier dose calculations than the other two medications. All three medications are human only treatments but are available as generics which makes the systemic treatment of *Malassezia* dermatitis much less expensive than it used to be.

There is a concerted effort internationally to substitute topical treatments for systemic treatments, and to use immunotherapy when appropriate, avoiding, as much as possible, the use of long-term systemic treatment; due to potential problems with resistance and side effects. That however is a topic for a later article as is the treatment of *Malassezia* dermatitis in cats.

Reading List (additional references supplied on request)

Negre A, Bensignor E, Guillot J. Evidence-based veterinary dermatology: a systematic review of interventions for *Malassezia* dermatitis in dogs. *Veterinary Dermatology* 20(1), 1–12, 2009