# Double-Blind, Placebo-Controlled Study to Evaluate Two Miconazole Conditioners for the Treatment of *Malassezia* Dermatitis in Dogs*

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## ABSTRACT

Eighteen dogs with *Malassezia* dermatitis participated in a clinical trial to evaluate the efficacy of miconazole conditioners. Dogs were randomly assigned to receive vehicle only, miconazole 1%, or miconazole 2% conditioner. Conditioners were used three times weekly for 2 weeks and then twice weekly for 2 weeks. Investigators evaluated erythema, pruritus, and yeast counts weekly. Owners scored pruritus daily. Yeast number decreased in all treatment groups. Yeast number in the vehicle group was higher than in both the miconazole treatment groups but was not different between the two miconazole groups. Clinical scores decreased but no difference was detected among groups.

## INTRODUCTION

*Malassezia pachydermatis* (*Pityrosporum canis*) is a common commensal organism of the anal sacs, auditory canal, anus, and skin of dogs.[1,2] This organism has been reported to cause skin disease in dogs.[3,4] In order for a commensal organism to become a primary pathogen, it must acquire virulence sufficient to overcome the normal host's defense, or in the case of *Malassezia* organisms, it has been hypothesized that the host's defenses are inadequate, overwhelmed, or dysfunctional.

*Malassezia* dermatitis is a common dermatologic disease of dogs and is usually associated with intense pruritus. The axilla and inguinal regions are commonly affected.[5] Erythema, lichenification, hyperpigmentation, and seborrhea are commonly seen in affected animals.[6] In most cases, *Malassezia* dermatitis is secondary to an underlying disease. Diagnosis is based on cytology and clinical response to antimycotic treatment.[7]

Systemic and topical therapies are currently used to treat canine *Malassezia* dermatitis.[8] Oral ketoconazole (Nizoral®, Janssen, Titusville, NJ) is effective but quite expensive, especially in large breed dogs, and has the potential for systemic adverse effects (e.g., hepatotoxicity). Oral itraconazole (Sporonox®, Janssen, Titusville, NJ) is also an effective treatment for *Malassezia*. It has less potential for adverse reactions but it is more expensive than ketoconazole. Topical therapy is also used to

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treat *Malassezia* dermatitis. It can be the only treatment (usually when financial constraints are present) or it can be used in conjunction with systemic treatment. Topical tar, selenium sulfide, and ketoconazole have been reported to be effective in killing *Malassezia* organisms.[9] In addition, miconazole has been reported to be effective against *Malassezia pachydermatis* in both in vitro and in vivo studies.[10–12]

Several miconazole-based products are currently available on the market in the USA but, to the best of the authors' knowledge, no placebo-controlled clinical studies have been performed to evaluate their efficacy. The purposes of this clinical trial were to (1) evaluate the efficacy of miconazole products compared with a vehicle conditioner and (2) to determine if there is a difference in efficacy of a 1% miconazole conditioner versus a 2% miconazole conditioner. The response to treatments was evaluated by cytology and clinical signs.

## MATERIALS AND METHODS

### Animals

Privately owned dogs diagnosed with *Malassezia* dermatitis were selected. Diagnosis was made based on suggestive clinical signs (e.g., pruritus, scaling, seborrhea oleosa) and cytology of the affected areas. *Malassezia* dermatitis was defined cytologically, based on the information available in normal dogs, as five or more yeast organisms per 2 square inches of a microscopic slide.[13–15] Cytologic preparations were made by direct slide impression on the skin or by using clear acetate tapes applied directly onto the skin. Slides were stained (Dif Quik) and examined under oil immersion (10 × 100).

To establish a diagnosis of *Malassezia* dermatitis, one slide was prepared from the most affected area of the body and the slide was evaluated in ten consecutive fields, counting the yeast organisms and calculating the average number per slide as is routinely done in a clinical situation. Once a diagnosis of *Malassezia* dermatitis was established based on the results of the first slide, four additional slides from other affected areas were prepared. The mean number of yeast organisms from all the sites was calculated. Cytology was repeated weekly throughout the study on the same body areas to monitor the response to therapy.

Superficial pyoderma, if present, was treated before the dogs entered the study. Criteria for diagnosis of superficial pyoderma included compatible clinical signs (papulopustular dermatitis), and suggestive cytology (degenerated polymorphonucleated cells and intracellular cocci). In affected dogs, standard treatment consisted of a 3-week course of oral cephalexin at 30 mg/kg twice daily. At the end of antibiotic treatment dogs were re-evaluated for the presence and severity of *Malassezia* dermatitis by cytology.

### Clinical Signs

Erythema and pruritus were graded and scored weekly by the investigator, while owners graded and scored pruritus daily (Tables 1 through 3). A five-point scale was used, with higher numbers signifying more severe clinical signs. An average score for the week was calculated based on the daily scores given by owners.

### Experimental Design

Once selected, dogs were divided into three groups. This division was randomized and blinded to the owner and the investigator. Group A received a placebo conditioner (vehicle used for the medicated conditioner) and the other two groups received miconazole leave-on conditioners (Resi-ZOLE®, Allerderm/Virbac, Fort Worth, TX—group B received 1%; group C received 2%). Owners were instructed to shampoo their dogs once weekly with a nonmedicated shampoo (Aller-

**TABLE 1. Criteria for the Evaluation and Scoring of Pruritus by the Owner**

| *Score* | *Definition* |
|---|---|
| 1 | Mild pruritus (scratching, rubbing, chewing, or licking for less than 10% of day) |
| 2 | Mild-moderate pruritus (scratching, rubbing, chewing, or licking for 10–30% of day) |
| 3 | Moderate pruritus (scratching, rubbing, chewing, or licking for 30–50% of day) |
| 4 | Moderate-severe pruritus (scratching, rubbing, chewing, or licking for 50–75% of day but still able to relax and sleep at night) |
| 5 | Severe pruritus (scratching, rubbing, chewing, or licking all the time—even at night and during a meal) |

**TABLE 2. Criteria for the Evaluation and Scoring of Pruritus by the Investigator**

| *Score* | *Definition* |
|---|---|
| 1 | No pruritus (no evidence of self trauma) |
| 2 | Mild-moderate pruritus (1–5 mild excoriations, involving only one part of the body) |
| 3 | Moderate pruritus (evident excoriations in more than one part of the body) |
| 4 | Moderate-severe pruritus (evidence of pyotraumatic dermatitis or deep ulcerations that are self-inflicted or scratching, licking, or chewing 1–5 times during the visit) |
| 5 | Severe pruritus (scratching, chewing, or licking constantly in the examination room; self-mutilation if left unattended) |

groom®, Allerderm), to apply the conditioner three times weekly for the first 2 weeks of the study, and then twice weekly for an additional 2 weeks. For the midweek treatments the animals were simply wetted before application of the conditioner without being shampooed. At the end of the trial, systemic treatment for *Malassezia* with oral ketoconazole at 5 mg/kg twice daily was administered to dogs whose *Malassezia* dermatitis did not resolve with the topical treatments.

**Statistics**

Data included the mean number of yeast organisms recovered from weekly cytologic specimens and changes in weekly scores of clinical signs. Data were analyzed for differences among treatment groups over time by tests for heterogeneity of regression. All data were analyzed at the highest significant order of regression. Differences among treatments were analyzed by least squares analysis of variance (LSANOVA) with the main effects of treatment, dog, week, and all appropriate interactions included in the

**TABLE 3. Criteria for the Evaluation and Scoring of Erythema by the Investigator**

| *Score* | *Definition* |
|---|---|
| 1 | Mild erythema (barely visible, involving less than 10% of the body) |
| 2 | Mild-moderate erythema (noticeable, involving 10–30% of the body) |
| 3 | Moderate erythema (easily noticeable, involving 30–50% of the body) |
| 4 | Moderate-severe erythema (evident, involving 50–75% of the body) |
| 5 | Severe erythema (evident, diffuse redness involving the entire body) |

**TABLE 4. Owner Scores of Pruritus**

| | *Mean ± SEM* | | | **P *values*** | | |
|---|---|---|---|---|---|---|
| ***Week*** | *Vehicle (A)* | *1% Miconazole (B)* | *2% Miconazole (C)* | *A versus B* | *A versus C* | *B versus C* |
| 0 | 3.33 ± 0.28 | 2.83 ± 0.32 | 2.33 ± 0.28 | .25 | .01* | .25 |
| 1 | 2.17 ± 0.28 | 2.50 ± 0.28 | 2.00 ± 0.28 | .41 | .67 | .21 |
| 2 | 1.83 ± 0.28 | 2.17 ± 0.28 | 7.83 ± 0.28 | .41 | 1 | .41 |
| 3 | 2.00 ± 0.28 | 1.83 ± 0.32 | 1.50 ± 0.28 | .70 | .21 | .44 |
| 4 | 2.08 ± 0.32 | 1.83 ± 0.32 | 1.32 ± 0.32 | .58 | .09 | .25 |
| *P* value: Weeks 0 versus 4† | .004* | .02* | .02* | | | |

Scores are expressed as mean ± standard error of the mean (SEM) and are indicated for each week and each treatment. Comparisons are done between treatments and between the beginning and the end of the study.
*Indicates statistically significant difference.
†Statistically significant differences were present between other weeks as well (see text for discussion). However, these comparisons were omitted from the table for purposes of simplification. Comparison of weeks 0 and 4 was deemed most important for illustrating study results.

model. Differences among treatments and weeks were tested using orthogonal contrast analysis. All data are presented as mean ± standard error of the mean (SEM). A *P* value of ≤.05 was considered significant.

## RESULTS

Eighteen dogs with *Malassezia* dermatitis completed the study. They were randomly assigned to one of the three treatments (n = 6, each treatment group). The dogs included four German shepherds, four Labrador retrievers, two cocker spaniels, one Jack Russell terrier, one golden retriever, two dachshunds, and two mixed-breed dogs. Ages ranged from 1 to 13 years, with an average of 7 years. Affected areas of the body (lesional areas where cytology was performed) included rear feet (n = 12), front feet (n = 12), groin (n = 11), axilla (n = 4), muzzle (n = 3), ventral surface of the neck (n = 4), periocular area (n = 2), lips (n = 2), ventral thorax (n = 1), pinna (n = 1), abdomen (n = 1), and ventral abdomen (n = 1). Sixteen dogs had underlying allergies of various types, as shown by further workup after the conclusion of the study, while two dogs had no evidence of underlying disease.

### Owner Scores of Pruritus

Tests for heterogeneity of regression indicated that the data were best described by a second order (quadratic) curve. Least squares analysis of variance at the second order indicated that within all treatments owner scores of pruritus changed significantly over time (Table 4). At the start of the study (week 0), the vehicle treatment group had a higher owner pruritus score than the group receiving the 2% miconazole treatment. However, there was no difference in pruritus scores between the treatments at any other time (week) during the study.

Within all treatments, owner pruritus scores improved over time. Week 0 was significantly

**TABLE 5. Investigator Scores of Pruritus**

| | *Mean ± SEM* | | | **P *values*** | | |
|---|---|---|---|---|---|---|
| ***Week*** | *Vehicle (A)* | *1% Miconazole (B)* | *2% Miconazole (C)* | *A versus B* | *A versus C* | *B versus C* |
| 0 | 3.50 ± .30 | 3.62 ± .33 | 3.00 ± .30 | .78 | .24 | .17 |
| 1 | 2.25 ± .34 | 2.67 ± .30 | 2.00 ± .30 | .36 | .58 | .12 |
| 2 | 2.05 ± .34 | 2.00 ± .30 | 1.83 ± .30 | .91 | .63 | .69 |
| 3 | 1.82 ± .39 | 1.65 ± .34 | 2.01 ± .38 | .73 | .73 | .47 |
| 4 | 2.02 ± .34 | 1.25 ± .34 | 1.21 ± .34 | .11 | .09 | .93 |
| *P* value: Weeks 0 versus 4† | .001* | .0001* | .0002* | | | |

Scores are expressed as mean ± standard error of the mean (SEM) and are indicated for each week and each treatment. Comparisons are done between treatments and between the beginning and the end of the study.
*Indicates statistically significant difference.
†Statistically significant differences were present between other weeks as well (see text for discussion). However, these comparisons were omitted from the table for purposes of simplification. Comparison of weeks 0 and 4 was deemed most important for illustrating study results.

higher than weeks 1, 2, 3, and 4 in the vehicle treatment group, and week 0 was significantly higher than weeks 3 and 4 in both of the miconazole treatment groups. There were no additional significant differences between the remaining weeks within all treatments.

**Investigator Scores of Pruritus**

Tests for heterogeneity of regression indicated that the data were best described by a second order (quadratic) curve. Least squares analysis of variance at the second order indicated that within all treatments, investigator scores of pruritus changed significantly over time (Table 5). However, there was no difference in pruritus scores between the treatments at any time (week) during the study.

Within all treatments, investigator pruritus scores improved over time. Scores at week 0 were significantly higher than the scores at weeks 1, 2, 3, and 4 for all treatments. There were no additional significant differences between the remaining weeks within the vehicle or 2% miconazole treatment groups. Within the 1% miconazole treatment group, scores at week 1 were also significantly higher than the scores at weeks 3 and 4.

**Investigator Scores of Erythema**

Tests for heterogeneity of regression indicated that the data were best described by a single order (linear) curve. Least squares analysis of variance indicated that within all treatments, investigator scores of erythema changed significantly over time (Table 6). However, there was no difference in erythema scores between the treatments at any time (week) during the study.

Within the vehicle treatment group, investigator scores of erythema were significantly higher at week 0 than at week 4. Within the 2% miconazole treatment group, investigator scores of erythema were significantly higher at weeks 0 and 1 than the scores at week 4. With-

**TABLE 6. Investigator Scores of Erythema**

| | *Mean ± SEM* | | | P *values* | | |
|---|---|---|---|---|---|---|
| ***Week*** | *Vehicle (A)* | *1% Miconazole (B)* | *2% Miconazole (C)* | *A versus B* | *A versus C* | *B versus C* |
| 0 | 2.67 ± 0.33 | 2.05 ± 0.37 | 2.50 ± 0.33 | .22 | .72 | .37 |
| 1 | 2.07 ± 0.38 | 1.67 ± 0.33 | 2.17 ± 0.33 | .42 | .85 | .29 |
| 2 | 1.67 ± 0.38 | 1.33 ± 0.33 | 1.83 ± 0.33 | .50 | .75 | .29 |
| 3 | 1.72 ± 0.43 | 1.06 ± 0.38 | 1.82 ± 0.43 | .26 | .86 | .19 |
| 4 | 1.59 ± 0.37 | 0.86 ± 0.38 | 1.03 ± 0.38 | .17 | .29 | .75 |
| *P* value: Weeks 0 versus 4† | .03* | .03* | .005* | | | |

Scores are expressed as mean ± standard error of the mean (SEM) and are indicated for each week and each treatment. Comparisons are done between treatments and between the beginning and the end of the study.
*Indicates statistically significant difference.
†Statistically significant differences were present between other weeks as well (see text for discussion). However, these comparisons were omitted from the table for purposes of simplification. Comparison of weeks 0 and 4 was deemed most important for illustrating study results.

in the 1% miconazole treatment group, the scores at week 0 were also significantly higher than the ones at week 4.

**Yeast Count**

Tests for heterogeneity of regression indicated that the data (Table 7) were best described by a second order (quadratic) curve. Least squares analysis of variance at the second order indicated that over all times there was no difference between the treatments, though it approached significance ($P = .0576$). Within all treatments, the vehicle treatment group had a significantly higher number of yeast organisms when compared with the 1% miconazole treatment group ($P = .001$) and the 2% miconazole treatment group ($P = .02$). Within all treatments, yeast counts decreased significantly over time. At week 0, there was no difference in yeast counts between treatments; however, at week 2 the vehicle treatment group had significantly higher yeast counts than those of both the miconazole treatment groups. Within the vehicle treatment group, the yeast counts at week 0 were significantly higher than at week 4; however, in both the miconazole treatment groups, counts at week 0 were significantly higher than at weeks 1, 2, 3, and 4. There were no other significant differences within the treatments.

## DISCUSSION

In this study both miconazole conditioners significantly decreased the number of yeast organisms after 2 weeks of treatment. Although the differences between the treatment groups were not statistically significant throughout the study ($P = .0576$), the vehicle treatment group had higher yeast counts than the other two groups at all weeks except week 0 (Table 7). At week 2 the difference between the vehicle and miconazole treatments was statistically significant. It is possible that if a larger number of dogs had been used in this study, the difference between treatments would have been more significant.

**TABLE 7. Yeast Counts (per high-power field)**

| | *Mean ± SEM* | | | **P *values*** | | |
|---|---|---|---|---|---|---|
| ***Week*** | *Vehicle (A)* | *1% Miconazole (B)* | *2% Miconazole (C)* | *A versus B* | *A versus C* | *B versus C* |
| 0 | 26.50 ± 4.88 | 23.50 ± 4.88 | 33.17 ± 4.88 | .66 | .33 | .16 |
| 1 | 17.67 ± 4.88 | 6.17 ± 4.88 | 12.00 ± 4.88 | .10 | .41 | .40 |
| 2 | 20.13 ± 5.45 | 2.00 ± 4.88 | 2.50 ± 4.88 | .01* | .01* | .94 |
| 3 | 12.82 ± 5.45 | 0.83 ± 4.88 | 1.53 ± 5.45 | .10 | .14 | .92 |
| 4 | 11.33 ± 4.88 | 1.17 ± 4.88 | 2.67 ± 4.88 | .14 | .21 | .82 |
| *P* value: Weeks 0 versus 4† | .03* | .002* | .0001* | | | |

Counts are expressed as mean ± standard error of the mean (SEM) and are indicated for each week and each treatment. Comparisons are done between treatments and between the beginning and the end of the study.

*Indicates statistically significant difference.

†Statistically significant differences were present between other weeks as well (see text for discussion). However, these comparisons were omitted from the table for purposes of simplification. Comparison of weeks 0 and 4 was deemed most important for illustrating study results.

No difference in efficacy was found between the two concentrations of miconazole. Based on the results of this study, a 1% miconazole product should be sufficient to treat *Malassezia* dermatitis and higher concentrations are not needed. It is interesting to note that the products that are commercially available contain 2% miconazole.

In our study no significant difference was found between treatments regarding the improvement of clinical signs. All dogs, including those in the placebo group, significantly improved at the end of the study. More specifically, owners' perception of pruritus indicated that even dogs receiving the placebo conditioner improved. This is probably because all dogs received regular bathing and flea control during the study though some of them might not have received similar treatment before the study.

In our study German shepherds and cocker spaniels were overrepresented, confirming breed predilection reported by other authors.[16,17] The vast majority of the dogs (16 of 18) in this study had underlying allergies, and the most commonly affected sites were the feet and groin. These findings are consistent with those of Bond et al who found a statistically significant higher number of *Malassezia* in the groin of atopic dogs.[15]

During the process of recruiting dogs for this study we found over 15 dogs that were initially highly positive for *Malassezia* (cytology from affected areas revealed more than 40 yeasts/high-power field) with concurrent superficial pyoderma that became negative for *Malassezia* after antibiotic treatment. Only a few dogs had a pure *Malassezia* dermatitis without additional skin infections. This made it more challenging to recruit a sufficient number of dogs for this study and also confirmed the hypothesized symbiotic relationship of mutually beneficial growth factors between *Malassezia pachydermatis* and staphylococci.[18] Nevertheless, the role of antibiotic therapy in the pathogenesis of

*Malassezia* dermatitis in dogs is reported as controversial in the literature. Some authors[14] have found that antibiotic therapy could be one of the factors associated with high *Malassezia pachydermatis* numbers in dogs, while others[15] found no significant differences in *Malassezia* population after antibiotic therapy.

Cytology was used in this study to monitor the disease because this is the most commonly used method to diagnose and monitor the dermatitis in a clinical setting,[7,18] though more sophisticated detergent scrub techniques have been developed.[19] Several techniques have been used to prepare cytologic specimens and, at the present time, there is no evidence that one is superior to another. Swabs, superficial skin scrapings, and tape impressions are all suitable ways to collect material. Sticky glass slides are now available as an alternative to tape.

Dogs in this study responded well to topical therapy, but eight dogs required systemic therapy at the conclusion of the study. Of the eight, four of these dogs were using the placebo conditioner, three were using the 2% miconazole conditioner, and one was using the 1% miconazole conditioner. The decision to start systemic therapy was based on both cytology and severity of the clinical signs because the number of yeast organisms seen on cytology relative to causation of clinical disease is controversial and varies among individuals. Some dogs can have a moderate number of yeast organisms on their skin and only mild clinical signs while others can have severe pruritus despite a low number of yeast organisms, suggesting the possibility of a hypersensitivity to *Malassezia* in allergic dogs.[8,20]

Miconazole is a synthetic imidazole derivative.[21] In humans it is used topically against a variety of skin, nail, and mucosal infections resulting from yeasts and dermatophytes.[21,22] It is particularly active against *Candida* species, *Trichophyton* species, *Epidermophyton* species, *Microsporum* species, and *Pityrosporon orbiculare* (*Malassezia furfur*) but it also possesses some activity against gram-positive bacteria. It is fungistatic at low concentrations and fungicidal at high concentrations.[22] The fungistatic effect correlates with inhibition of ergosterol synthesis and elevated lanosterol/ergosterol ratios in the sensitive organisms.[23] The fungicidal effect involves rapid membrane damage and is unrelated to the imidazole-induced block in ergosterol synthesis.[23] Miconazole, at doses that can be reached only by topical application, exerts its antibacterial and fungicidal activity not only by inhibiting ergosterol synthesis and fatty acid elongation plus desaturation[24] but also by inducing changes in the cellular organization of lipids.[25]

## CONCLUSION

Miconazole is well tolerated in humans after topical application.[26] Miconazole also appears to be well tolerated in dogs because none of the dogs recruited in this study had any adverse effect with this therapy. Ketoconazole, itraconazole, and fluconazole are all effective against *Malassezia.*[7] However, all these drugs are quite expensive and have the potential for adverse effects. Topical therapy has the advantage of being extremely safe and relatively inexpensive.

In summary, both miconazole 1% and 2% leave-on conditioners were equally effective in decreasing *Malassezia pachydermatis* on the skin of dogs in this study. Yeast counts in the vehicle group were higher than those of both miconazole treatment groups, which had similar yeast counts after treatment. Miconazole leave-on conditioners are a well-tolerated and effective adjunctive treatment for *Malassezia* dermatitis in the dog.

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