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Efficacy of itraconazole in 18 cases of *Malassezia* dermatitis in dogs

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Abstract: Itraconazole was found to be an effective antifungal for the treatment of canine *Malassezia* dermatitis (MD). MD was diagnosed in 18 dogs, which were treated with itraconazole administered orally at 5 mg/kg of body weight, q12hrs, for 21 to 30 days. High prevalence breeds of MD were Maltese (22%), Cocker Spaniel (17%), Pekingese (11%), and Vizsla (11%). The dermatological signs of *Malassezia* dermatitis were crust (31%), alopecia (25%), hyperpigmentation (25%), scales (19%), erythema (13%), lichenification (11%), pustule (11%), ear swelling (11%), papules (5%), and offensive odor (5%). Commonly affected areas were ear canal (41%), axillae (18%), groin (15%), perianal (12%), ventral aspect of the neck (9%), interdigital spaces (1%), and muzzle (1%). Sixty seven percent of dogs with MD had cocci. Clinical responses of itraconazole were seen good, moderate, no responses of itraconazole, in 89%, 0%, and 11%, respectively, according to the owner's satisfaction to follow up call. Recurrence was detected on five good responsive dogs and adverse effects of the treatment were detected in only one dog. On the basis of this clinical study, itraconazole is a good choice in the treatment of canine *Malassezia* dermatitis. Efficacy, frequency of administration and veterinary approval are the major advantages.

Key words : *Malassezia* dermatitis, itraconazole, dog.

Introduction

Malassezia pachydermatis is the first recognized as a cause of dermatitis in dogs about 30 years ago. It was not until the 1990s that *Malassezia* dermatitis in dogs became a subject of heightened veterinary interest[3,9,14,20]. *M. pachydermatis* has also been implicated as an opportunistic secondary pathogen on the skin of dogs affected by numerous dermatitis which may include allergic disease, keratinization disorders, bacterial skin disease, endocrine disease (especially hypothyroidism) as well as long-term corticosteroid or antibiotic administration[1,8,13,20,21]. These predisposing factors that alter the skin surface microclimate such as excessive sebum or cerumen production, moisture accumulation, and disruption of the epidermal barrier[11,20,21]. *Malassezia dermatitis* is typically intensely pruritic, but the only primary lesion produced is erythema. Secondary lesions include excoriations, seborrheic plaques, lichenification, maceration, and intertrigo[8,13,14,23]. *Malassezia* spp commonly found in the ear canal, anal sacs, interdigital areas, lip, rectum and vagina of dogs[5,8,21].

Therapy of *M pachydermatis* infection must be eliminated both the yeast and predisposing problems facilitating yeast overgrowth. Topical and systemic therapy are helpful in reducing the populations of *Malassezia* spp from the skin and the most rapidly effective[11,20,21]. However, only topical treatment may fail to completely resolve the infection, because of failure to comply with the labor-intensive regimen that is required[8]. Systemic treatment is the most effective method for *Malassezia* dermatitis. Antimycotic agents have been recommended are ketoconazole, itraconazole, and fluconazole[4,7,8,13,20-22]. Itraconazole is a triazole derivative of the azole group of drugs. It acts by altering fungal cell membrane permeability through inhibition of ergosterol synthesis. It is lipophilic and keratophilic triazole antifungal agent approved for treatment of cutaneous and systemic fungal diseases[2,4,7,8]. Owing to these properties, the drug concentration of skin and nail exceeds the corresponding plasma concentration by these properties[2]. As a result, itraconazole is the appropriate choice for the treatment of nails and skin infection[10].

The purpose of the study reported here was to determine clinical efficacy of itraconazole for the treatment of cutaneous *M. pachydermatis* infection in dogs.

Materials and Methods

Eighteen privately owned dogs were included in the study (Table 1). Malassezia dermatitis was diagnosed based on history, clinical signs, and cytologic evidence for at least 1 body site having a mean of 1 yeast organism/oil immersion field (OIF).

Cytological examination were performed for the diagnosis of MD on the skin by direct impression smears, tape impressions smears, skin scraping, and ear swab using modified Wright stain (Diff-Quik® International Reagent Corp., Japan). The number of *Malassezia* spp. was counted on 10 random high-power fields (×1000) and the grade was made according to the following scheme; grade 1, < one per field; grade 2, 2 to 3 per field; grade 3, > 4 and <10 per field; or grade 4, 10 per field. For the cocci samples were collected, stained, and

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Table 1. Clinical findings and improvement in *Malassezia* dermatitis dogs treated with itraconazole

Dog	Breed	Age (yr)	Gender	Lesions	Clinical Improvement	Recurrence
1	Daschhund	1	Male	A, P, Pr, S	Good response	No
2	Tosa	3	Male	A, Pr	No response	No
3	Pekinese	5	Male	A, Pr, Pu	Good response	Yes
4	Maltese	9	Male	O	Good response	No
5	Maltese	1	Male	Pr	Good response	Unknown
6	Vizula	1	Male	A, EC, H, Pr, Pu, S	Good response	Unknown
7	Cocker Spaniel	3	Female	E	Good response	Unknown
8	Vizula	3	Male	A, Pr	Good response	No
9	Pekinese	1	Female	A, C	Good response	Yes
10	Japanese Chin	1	Female	Pr, S	Good response	No
11	Cocker Spaniel	5	Male	C, E, G, S, Pr	Good response	No
12	Yorkshire terrier	10	Female	A, Pr, S	No response	No
13	Cocker Spaniel	2	Female	C, E, G, H	Good response	Yes
14	Mixed	3	Female	C, L, H	Good response	No
15	Poodle	3	Female	C, Pr	Good response	Unknown
16	Maltese	8	Female	A, C, Pr	Good response	No
17	Pug	3	Male	E, G, H, P, Pr	Good response	Yes
18	Maltese	3	Male	Pr	Good response	Yes

A; Alopecia, C; Crust, E; Erythema, EC; Epidermal Collarette, H; Hyperpigmentation, L; Lichenification, O; odour, S; Scaling, G; Greasy exudates, P; Papules, Pr; Pruritus, Pu; Pustule,

counting of cocci used the same methods of *Malassezia*. The slide from each site was graded according to the following scheme; 0: absent, 1: mild, 2: moderate, 3: severe.

All dogs were treated orally with itraconazole at 5 mg/kg twice daily with food. Itraconazole capsules were reformulated for each dog.

Response to itraconazole was scored on a scale of 1-3; 1= No response; the pruritus and dermatological lesions, which are characterized by diffuse erythema, greasy surface exudates, scale and crust, were unchanged; 2= Moderate response; Less than 50% improvement in pruritus and/or dermatological lesions; 3= Good response; More than 50% improvement in pruritus and dermatological lesions.

Results

Age ranged from as young as 1-4 months (four dogs) to as old as 10 years (one dog). The median age was 3.6 years. There were 8 female (44%) and 10 male dogs (56%). Maltese (22%), Cocker Spaniel (17%), Pekingese (11%), and Vizsla (11%) were the most commonly diagnosed as having *Malassezia pachydermatis*. Other breeds were included Dachshund, Tosa, Japanese Chin, Yorkshire terrier, Poodle, Pug and mixed breed.

In cytologic examination, fifteen dogs were more than grade II. Of these, the numbers of dogs with a highest grade of II, III, or IV were 7, 1, and 7, respectively. Cocci were detected on 12 dogs concurrently.

Otitis externa was present in 14 (78%) dogs. Cocker Spaniel (17%), Maltese (11%) and Pekingese (11%) were at greatest incidence for otitis externa. Five (28%) cases were only presented in otitis externa without any skin disorders.

Pruritus (93%) was a major sign in sixteen cases except only one case that was 3-year-old female Cocker Spaniel with IV grade. The other signs were crust (31%), alopecia (25%), hyperpigmentaion (25%), lichenification (11%), scale formation (19%), erythema (13%), pustule (11%), ear swollen (11%), papule (5%), and offensive odour (5%). Commonly affected areas were ear canal (41%), axillae (18%), groin (15%), perianal (12%), ventral aspect of the neck (9%), interdigital spaces (1%), and muzzle (1%).

Sixteen dogs treated with itraconazole exhibited good response accounting for 89% of treatment rate. Nine dogs (50%) were considered 'cured'. They showed more than 50% improvement in pruritus and dermatological lesions without recurrence. Moderate response was not seen. Only two dogs

showed no response for the treatments. Of 16 good response dogs, five (31%) were recurrent. Any adverse effects were not seen except one dog which showed anorexia and depression.

Discussion

No age predilection has been demonstrated by other investigators[12,21], but we found that 67% of our cases were 1-3 years old. The prevalence may be proportioned to the hospital population of age. The number of male dogs (56%) was superior to female (44%). Two investigators have also found similar results that spayed females and castrated males to be at increased risk[12,17]. The significance of these finding are not presently known.

Predisposed breeds such as West Highland white terrier, Basset hound, American Cocker spaniel, Shih Tzu, English setter, and Dachshund were not common in the general hospital population with the exception of Cocker Spaniel and Dachshund[13,21]. In this study, other breeds reported to be at risk include Maltese, Cocker Spaniel, Pekingese, and Vizsla. The prevalence of MD may be proportioned to hospital population.

For the semiquantitative analysis of *Malassezia* dermatitis the number of *Malassezia* spp was counted on 10 random high powered fields[18,19]. The prevalence of higher *Malassezia* spp. number did not correlate significantly with sample site, sex, or age[17]. In this study, 6% of patients were included grade 0 and 94% were included more than grade II. In spite of low grade results of cytologic examination they showed the clinical signs and dermatological lesions. It was indicated that small number of *Malassezia* spp may have role of pathogenesis of *Malassezia* dermatitis which cause the clinical signs and lesions. It has been reported that some atopic dog with MD had an IgE-mediated type I hypersensitivity reaction to intracellular protein extracts of *M pachydermatis*, since some animals show extreme pruritus and other clinical signs when relative few organisms are detectable[14,20]. Therefore, most dermatologists should consider more than 1 to 2 organisms per oil immersion field as significant.

Generalized MD is characterized by diffuse erythema, with greasy surface exudates, scale (yellow and/or slate grey) and crust. They often have offensive, rancid or yeast odour[8,22]. Chronic cases can have hyperpigmentation and lichenification. Localized lesions may occur, with involvement of the ear, periocular, lip fold, muzzle, interdigital, ventral neck, axillary regions, medial thighs, perianal region and intertrigious areas[8,11,19,20]. The results of this study were consistent with the findings of other investigators concerning the dermatological signs and affected area of *Malassezia* dermatitis. However, *M pachydermatis* were rarely found in interdigital spaces in this study.

Itraconazole administration (5 mg/kg every 12 hours) was efficacious in the treatment of MD in dogs. In this study 2 cases showed no response, which one was diagnosed as hypothyroidism and the other with IV grade was treated only 7 days. Recurrence was detected in 5 cases and the recurrence was not evaluated in 4 cases due to the losing and selling. The reasons of recurrence were known due to ongoing skin disorder, especially endocrine disease (hypothyroidism), hypersensitivity diseases (atopy, food hypersensitivity), and keratinization defects (seborrhea)[9,10,15,21]. However, every cases of systemic therapy of itraconazole exhibited a good response except 2 cases. Furthermore, itraconazole individual administration exhibited more than 50% improvement in pruritus and clinical lesions. After one-week of itraconazol administration 91% of patients exhibited a good response. To increase clinical improvement, therapy should be continued for 7 to 10 days beyond clinical care. An average duration of treatment was 4 weeks.

In human medicine, itraconazole is a lipophilic agent that result in retention of the drug in the skin, not found in body fluid[2,8]. The drug is administered orally, and the principal routes of delivery to the stratum corneum include excretion, passive diffusion, and transfer via the sebum[8]. Clinical trials have demonstrated that itraconazole concentrations remain high in the skin and nails after treatment for dermatomycosis or onchomycosis for up to 2 weeks and 3 months, respectively, after the end of therapy. It has also been reported that incorporation of itraconazole in the sebum and stratum corneum enables itraconazole to be detected in the skin surface for 3 to 4 weeks after administration is discontinued[1]. Therefore, it has the potential to be useful for the treatment of cutaneous and otic *M pachydermatis* infection in dogs. The pharmacokinetic profile of itraconazole oral administration suggests that pulse administration, intermittent administration of a drug at the recommended dose with a longer interval between doses, could be as efficacious as once daily. Compared with daily administration, the benefits of pulse administration include decreased potential for side effects, increased owner compliance, and reduced treatment cost. Further studies are required to establish the efficacy and potency of pulse administration of itraconazole in dogs.

Conclusion

Results suggested that itraconazole administration were effective in the treatment of MD. However, recurrence of the MD was occurred in the cases having uncontrolled underlying disorders. Therefore, successful management maybe needed to these cases combined with the specific treatments for the underlying causes.

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개에서 *Malassezia* 피부염에 대한 itraconazole 치료 18례

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요 약: *Malassezia* 피부염으로 진단된 18두의 개를 대상으로 Itraconazole 5 mg/kg을 1일 2회 경구 투여하여 치료효과를 알아 보았다. 치료반응을 보인 환자는 88%이었으며 소양감과 피부병변은 치료후 1주일에 확연히 개선되었다. 치료대상견의 품종은 Maltese(22%), Cocker Spaniel(17%), Pekingese(11%), Vizsla(11%)이었다. 피부증상으로는 가피(31%), 탈모(25%), 색소침착(25%), 인설(19%), 발적(13%), 태선화(11%), 농포 (11%), 귀부종(11%), 구진(5%)의 순으로 나타났다. 병변발생부위는 이도(41%), 액와부(18%), 서혜부(15%), 회음부(12%), 복측경부(9%), 지간부(1%), 총구부(1%) 이었다. 세포학적 검사시 61%의 환견에서 구균이 동시에 검출되었다. Itraconazole에 대한 임상반응은 89%가 치료반응을 보였고 (2두)11%는 치료반응을 보이지 않았다. 치료반응을 보인 환자 중 5두는 재발되었고 1두는 갑상선 기능저하증이었으며 나머지 4두는 재발의 원인을 확인할 수 없었다. 1두에서 투여후 28일에 식욕결핍, 침울의 증상이 발현되어 투약을 중지하였다. 따라서 itraconazole을 5 mg/kg을 1일 2회 경구투여는 *Malassezia* 피부염에 효과적인 치료로 사료된다.

주요어: *Malassezia* dermatitis, itraconazole, dog.