COMPARATIVE THERAPEUTIC EFFICACY OF GRISEOFULVIN AND FLUCONAZOLE IN CANINE DERMATOPHYTOSIS

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ABSTRACT

A clinico-therapeutic study was conducted on 12 dermatophytosed dogs brought to TVCC, Pantnagar. Two groups of 6 dogs each were formed. Efficacy of oral Griseofulvin and fluconazole in dermatophytosis was evaluated. The clinical examination of the dogs was followed every 7 days till complete cure and hemato-biochemical evaluation before and after treatment was performed. Griseofulvin was found superior to fluconazole in treatment of canine dermatophytosis on the basis of disappearance of clinical manifestations, recovery rate post treatment, hematological and biochemical profiles. Moreover, fluconazole increased the activity of ALT that indicated hepatocellular damage.

KEY WORDS: Mycotic Dermatitis, Canine, Dermatophytes, Griseofulvin, Fluconazole

INTRODUCTION

The dogs are considered the most intelligent and loyal pet animal to the mankind. During their service to the mankind, they suffer with so many ailments (Hirt, 2011). Skin diseases are among the commonly encountered problems in dogs. Dermatophytosis has an important role in these skin problems and is one of the most common infectious diseases of canines. It has zoonotic implication too. It is a superficial infection of the keratinized tissues including nails/claws, hair and stratum corneum of the skin, primarily caused by two species of fungi: *Microsporum* and *Trichophyton*. Many drugs have been used both locally and orally in the treatment of dermatomycosis. A protracted skin disease is often difficult to control due to its chronicity and recurrence, and may require persistent efforts and long duration of therapy. Therefore the present study was planned to compare the effect of two antifungals (griseofulvin and fluconazole) against canine dermatophytosis.

MATERIALS AND METHODS

Animals attending Teaching Veterinary Clinical Complex, Pantnagar for various skin infections were routinely subjected to clinical examination. Skin scrapings were collected from affected areas and fungal spores were detected at the end of microscopic examinations. Both direct microscopic examination and cultural stiudies were carried out. Twelve dogs irrespective of sex, age suffering from mycotic dermatitis were included in the present study. They were divided into two groups of six dogs each. Dogs of Group 1 were treated with griseofulvin orally at the dose rate of 25 mg/kg bid for 20 days and dogs of Group 2 were treated with fluconazole orally at the dose rate of 5 mg/kg bid for 20 days. Six healthy dogs were included in the study as control for comparison.

The supportive treatment included anti-histaminic (chlorpheniramine maleate @ 2 mg/kg b.wt. i/m od) and fatty acids supplement (Nutricoat Advance® @ 5 ml per os bid for pups and 10 ml per os bid for adult dogs for 15-30 days).

The blood and serum samples of the dogs were collected on day 0 and then after the cessation of therapy in various groups to evaluate the effect of the treatment. About 2 ml of blood sample

was collected from cephalic vein of each dog, immediately after collection, blood was transferred to EDTA(1 mg /ml) vials for the analysis of blood glucose, protein profiles, and enzymes following standard laboratory procedures.

Therapy evaluation

The therapeutic efficacy of formulations was evaluated on the basis of significant variation in hemato-biochemical profiles, the disappearance of clinical manifestations and skin scraping examination . Statistical analysis of the data was done using statistic software SPSS 16.0. Data pertaining to hematological and biochemical profiles was analyzed by t-test and ANOVA technique to test the significance of means as per the method described by Snedecor and Cochran (1994).

RESULTS AND DISCUSSION

On treatment of affected dogs with griseofulvin, fungal spores and macroconidia disappeared by day 21 from skin scrapings of all the dogs along with pruritis, nodules, hyperpigmentation whereas symptoms of alopecia, erythema, hyperkeratosis, folliculitis, broken hair and rough hair coat resolved on day 14 (Table 1). In four dogs, complete disappearance of clinical manifestations was observed on day 21 of initiation of therapy. ESR and TLC values were found significantly high ($P<0.05$) in both groups 1 and 2 before treatment in comparison to healthy control group , both ESR and TLC returned to normal values after treatment on day 28 (Table 2) .

Table 1a Therapeutic assessment of oral griseofulvin (n=6)

Clinical examination of skin	0^{th} day	7^{th} day	14^{th}day	21^{st} day	28^{th}day	35^{th}day
Presence of fungal structures (spores/macroconidia/hyphae)	++ (5)	++(4)	+(2)	+(1)	-	-
Patches of alopecia	++ (4)	++(2)	+(1)	-	-	-
Pruritis	++(5)	++(4)	++(2)	++(1)	-	-
Papules	+++	++(3)	-	-	-	-
Nodules	+++	+(5)	++(3)	+(2)	-	-
Erythema	+	+(4)	+(2)	-	-	-
Scales	++	++(5)	+(3)	+(1)	-	-
Hyperpigmentaion	++	++(5)	+(3)	+(1)	-	-
Hyperkeratosis/ Lichenification	++(2)	++(2)	+(1)	-	-	-
Broken hair	++	++(5)	+(2)	-	-	-
Rough hair coat	+	++(5)	+(2)	-	-	-
Folliculitis/ furunculosis	+++(4)	++(4)	++(2)	-	-	-

Figures in parenthesis indicate the number of dogs affected

There was a significant variation in protein profile during infestation . Total protein and globulin levels were significantly increased , albumin and A:G ratio significantly decreased during infestation which turned to normal level after treatment in both the groups on 28 th day (Table 3) . The overall recovery was 100% (Plate 1). Balda *et al.* (2007) reported the efficacy of griseofulvin to be 100% in dermatophytosis with no side effects which is in corroboration with the present study. Griseofulvin interferes with mitosis, as a result of which multinucleated and stunted fungal hyphae results from its action. Because it is fungistatic, the newly formed keratin is not invaded by the fungus. It persists for weeks in skin and keratin preventing the infection to recur after treatment (Tripathi, 2003).

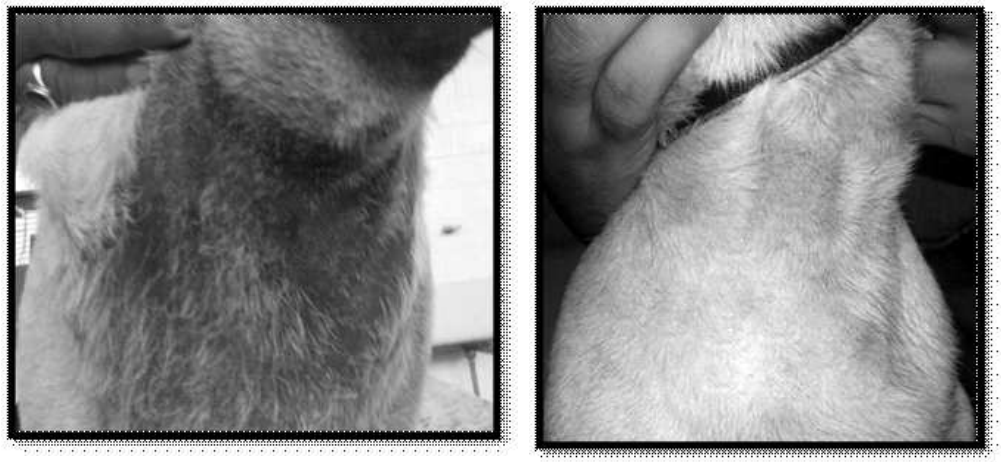

Plate 1.Therapeutic effect of griseofulvin on mycotic dermatitis in dog

a) pre treatment b) post treatment

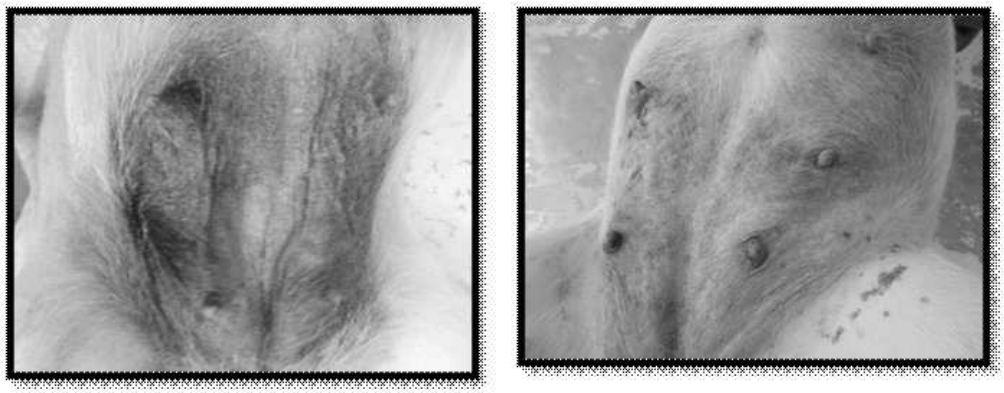

Plate 2.Therapeutic effect of fluconazole on mycotic dermatitis in dog

a) pre treatment b)post treatment

Table 1 b Therapeutic assessment of oral fluconazole (n=6)

Clinical examination of skin	**0th day**	**7thday**	**14thday**	**21stday**	**28thday**	**35thday**
Presence of fungal structures	++	++(4)	+(3)	+(2)	+(1)	++(1)
Patches of alopecia	++ (5)	++(4)	+(2)	+(1)	+(1)	++(1)
Pruritis	++(3)	++(2)	++(1)	-	-	-
Papules	+++	++(4)	++(2)	-	-	-
Nodules	+++	+(5)	++(3)	+(2)	+(1)	-
Erythema	+	+(4)	+(2)	+(2)	-	-
Scales	++	++(5)	++(2)	+(2)	-	-
Hyperpigmentaion	++	++(5)	++(3)	+(1)	-	
Hyperkeratosis/ Lichenification	++(2)	++(2)	+(1)	-	-	
Broken hair	++	++(5)	+(2)	-	-	
Rough hair coat	+	+(5)	+(1)	-	-	
Folliculitis/ furunculosis	+++(4)	++(4)	+(2)	+(1)	-	

Figures in parenthesis indicate the number of dogs affected

In group 2, where oral fluconazole was given to affected dogs, the improvement in clinical manifestations started on day 7. Pruritis, papules, lichenification and broken hair resolved by day 21 in all dogs (Table 4). There was evidence of fungal spores in 2 cases on day 21 and one dog remained affected even after 35 days of therapy. One dog did not show complete recovery. Affected hematological parameters returned to normal post treatment (Table 2).

Table 2 Therapeutic effect (Mean±SE) of the three treatments against mycotic dermatitis on hematological attributes of the treated dogs

Parameters			Group 1 (Griseofulvin)		Group 2 (Fluconazole)	
		Healthy(n=6)	BT (0^{th} day)	AT(28^{th}day)	BT (0^{th} day)	AT (28^{th} day)
Hb (g/dl)		15.034±0.39[a]	13.97±0.22 [a]	14.3±0.42 [a]	13.83±0.67 [a]	14.33±0.46 [a]
PCV (%)		45±1.73[a]	43.83±2.09 [a]	44±0.52 [a]	43±1.53 [a]	40.67±1.26 [a]
ESR (mm/h)		4.17±0.48[a]	7±0.36 [b]	4.5±0.22 [a]	7.67±0.49[b]	4.17±0.31 [a]
TEC (10^6/cumm)		7.94 ±0.42[a]	8.29±0.59 [a]	8.13±0.33 [a]	7.76±0.45 [a]	7.56±0.24 [a]
TLC (10^3/cumm)		11.23±0.88[a]	15.96±0.34 [b]	11.79±0.29 [a]	16.60±0.44 [b]	12.47±0.32 [a]
DLC (%)	**N** (%)	70.17±2.69[a]	71±1.03 [a]	69.5±1.28 [a]	69±1.09 [a]	69.67±1.02 [a]
	E (%)	4.84±0.31[a]	4.67±0.67 [a]	4.83±0.30 [a]	4.67±0.49 [a]	4.34±0.33 [a]
	L (%)	20.5±2.78[a]	17.17±2.24 [a]	21.33±1.17 [a]	22.17±0.83 [a]	22.67±1.20 [a]
	B (%)	0.5±0.23[a]	0.5±0.22 [a]	0.33±0.21 [a]	0.5±0.22 [a]	0.17±0.16 [a]
	M (%)	4±0.25[a]	3.67±0.33 [a]	4±0.36 [a]	3.67±0.42 [a]	3.17±0.31 [a]

Figures having different superscripts across the columns are significantly different upto 5% level of significance.

As in group 1 there was a significant variation in protein profile during infestation .Total protein and globulin levels were significantly increased , whereas albumin and A:G ratio significantly decreased ,which returned to normal level as in group 1 after treatment on 28th day.

Table 3 Therapeutic effect (Mean±SE) of the three treatments against mycotic dermatitis on biochemical attributes of the treated dogs

Parameters		Group 1 (Griseofulvin)		Group 2 (fluconazole)	
	Healthy(n=6)	BT (0^{th} day)	AT(28^{th} day)	BT (0^{th} day)	AT(28^{th}day)
Glucose (mg/dl)	91.83±4.53[a]	95.67±4.30 [a]	97.16±3.73 [a]	93.67±4.72 [a]	96.34±4.75 [a]
Total Protein(g/l)	67.25±0.47[a]	79.83±0.72 [b]	69.34±0.74 [a]	80.24±0.89 [b]	68.79±0.70 [a]
Albumin (g/l)	33.64±0.59[a]	25.74±0.49 [b]	33.04±0.59 [a]	25.04±0.40 [b]	32.07±0.59 [a]
Globulin (g/l)	33.61±0.95[a]	54.08±1.05 [b]	36.31±0.77 [a]	55.19±0.87 [b]	36.72±1.23 [a]
A:G ratio	1.07±0.04[a]	0.48±0.01 [b]	0.91±0.02 [a]	0.45±0.01 [b]	0.88±0.04 [a]
ALT (IU/l)	58.66±5.25[a]	61.83±5.25 [a]	64.5±4.12 [a]	63±4.07 [a]	77.5±1.23 [b]
AST (IU/l)	47±2.62[a]	45.67±3.92 [a]	47.17±1.42 [a]	42.33±2.56 [a]	47.5±2.14 [a]

Figures having different superscripts across the columns are significantly different upto 5% level

In recovered dogs there was significant decrease ($P<0.05$) in serum total proteins, albumin and A:G ratio and decrease in globulins on day 28 after initiation of treatment (Table 3). Five out of six dogs recovered completely by day 28 following treatment with fluconazole. The overall recovery

was observed to be 83.33% (Plate 2). Fluconazole inhibits the fungal cytochrome P_{450} enzyme lanosterol demethylase and thus impairs ergosterol synthesis leading to a cascade of membrane abnormalities in the fungus. It is water soluble, not affected by food or gastric pH, hence better absorption than griseofulvin (Tripathi, 2003). Further fluconazole showed the increased activity of liver specific enzyme alanine amino transferase (ALT) post treament that indicated hepatocellular damage after treatment.

Although, fluconazole is effective against dermatophytes, but efficacy against *Aspergillus spp.* is doubtful (Sandhu and Rampal, 2011). In general fluconazole appears to have a wider range of antifungal activity than ketoconazole. Its oral bioavailability is not affected by food or gastric acid unlike ketoconazole. Also it has fewer side effects and better tolerated than ketoconazole (Sandhu and Rampal, 2011). Fluconazole is also effective against *Malassezia pachydermatis*, the most commonly isolated yeast (Brito *et al.,* 2009). Therapeutic levels persist in stratum corneum for 10 days after the therapy is stopped. Because fluconazole is the fungal enzyme specific antifungal drug of the 3 systemic azoles (Ketoconazole, itraconazole and fluconazole), side effects are rare (Muller, 2001).

On the basis of evaluation procedure outlined in this study, therapeutic gradation was made and griseofulvin was graded superior treatment for fungal dermatitis than fluconazole on the basis of resolution of clinical manifestations, recovery rate and improvement of hemato-biochemical profiles.

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