

Use of lufenuron for treating fungal infections of dogs and cats: 297 cases (1997-1999)

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Objective—To evaluate use of lufenuron for treating cutaneous fungal infections in dogs and cats.

Design—Retrospective study.

Animals—156 dogs and 201 cats with dermatophytosis or superficial dermatomycoses.

Procedure—Medical records were reviewed for dogs and cats that had been treated for dermatophytosis or other fungal infections by administration of lufenuron and 18 dogs and 42 cats that were not treated and served as a control group.

Results—Dogs were treated once by oral administration of lufenuron tablets at doses ranging from 54.2 to 68.3 mg/kg (24.6 to 31.0 mg/lb) of body weight. Samples of skin, scrapings, and hair were obtained daily from 14 dogs with dermatophytosis; mean durations from time of treatment to time of negative fungal culture results and resolution of gross lesions were 14.5 and 20.75 days, respectively. In all treated dogs, gross lesions resolved within approximately 21 days. Cats were treated once by oral administration of lufenuron suspension in doses ranging from 51.2 to 266 mg/kg (23.3 to 120.9 mg/lb). Samples were obtained daily from 23 cats; mean durations from time of treatment to time of negative fungal culture results and resolution of gross lesions were 8.3 and 12 days, respectively. Time to resolution of lesions in most untreated control animals was approximately 90 days. Adverse effects of treatment were not detected.

Conclusions and Clinical Relevance—Results of this study suggest that lufenuron provides an effective, convenient, and rapid method for treating fungal infections in dogs and cats. (*J Am Vet Med Assoc* 2000;217:1510-1513)

Dermatophytes are classified on the basis of their morphologic characteristics^{1,2} and include *Microsporum*, *Trichophyton*, and *Epidermophyton* spp, all of which are pathogenic for humans and animals.² Three species, *M canis*, *M gypseum*, and *T mentagrophytes*,³ cause most clinical cases of dermatophytosis in dogs and cats.⁴

Microsporum canis is the most common cause of ringworm and is transmitted from cats and dogs to humans.^{3,5} Spontaneous remission of dermatophytosis in companion animals often occurs within 1 to 3 months, whereas treatment is undertaken to reduce transmission to other animals, including humans, and eradicate the infection.⁶ Dermatomycoses that affect companion animals include nondermatophytic superficial fungal infections with organisms such as *Aspergillus*, *Candida*, *Malassezia*, and *Trichosporon* spp.

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Traditionally, fungal infections have been treated with griseofulvin and ketoconazole.

Lufenuron⁷ is classified as an insect development inhibitor because of its ability to inhibit chitin (a polymer of N-acetylglucosamine) synthesis, polymerization, and deposition. It is used in veterinary medicine as a flea control treatment, administered orally once per month. Chitin constitutes 25 to 50% of the dry weight of fleas.⁸ After administration, lufenuron is dispersed to adipose tissue and slowly released into the bloodstream. During a blood meal, a female flea ingests lufenuron, which is transferred to the eggs. Eggs containing lufenuron may desiccate, because their structural integrity is disrupted. The chitin-containing egg tooth fails to develop normally, and many larvae cannot hatch and die in the egg. Larvae that hatch from treated eggs die during the first larval molt.⁹

Fungal cells are also surrounded by cell walls composed of complex polysaccharides, primarily chitin, chitosan, glucan, and mannan. The efficacy of orally administered antifungal preparations for systemic treatment such as griseofulvin demonstrates that drugs given orally can reach fungal cell walls by penetrating keratinized tissue.

Our interest in lufenuron was aroused following a systematic computer analysis of 4,269 case records of animals admitted to our clinic. At that time, 531 animals (429 dogs, 102 cats) had been treated for flea infestations by administration of lufenuron, and 116 (62 dogs and 54 cats) had been treated for dermatophytoses with recommended antifungal drugs. Importantly, none of the animals being treated for flea infestations were being treated for fungal infections. This unusually sharp distinction between the 2 groups of animals, dogs and cats alike, led us to conjecture that lufenuron has antifungal properties of therapeutic importance that may be attributable to its proven antichitin properties. We therefore began treating dogs and cats that had dermatophytoses or superficial dermatomycoses with lufenuron. The purpose of the study reported here was to evaluate the use of lufenuron for treating fungal infections in dogs and cats.

Criteria For Selection Of Cases

Medical records of dogs and cats with dermatophytosis or superficial dermatomycosis that were evaluated at our hospital between 1997 and 1999 and treated by administration of lufenuron were reviewed. Medical records of dogs and cats that had dermatophytosis and received no treatment were also reviewed to provide a control population.

Procedures

Evaluation of lesions—Untreated control animals were evaluated by use of physical examination and fun-

gal culture at time of initial referral and were then examined for signs of spontaneous recovery (regrowth of hair, remission of lesions such as scaling and crusts) by use of physical examination on a weekly basis. Treated animals were evaluated by use of physical examination and fungal culture at time of initial referral before treatment. For certain animals, samples for fungal culture were obtained daily until negative results were obtained; fungal cultures were then performed on a weekly basis for 6 to 8 weeks. Clinical recovery was deemed the resolution of all clinical signs related to mycotic infection and regrowth of affected hair. Mycotic infection was deemed to be cured when 2 consecutive negative culture results were obtained, with a 4-week period between the negative culture results.

Laboratory analyses—Hair and skin scraping specimens were collected, according to the protocol detailed by Kirk and Bister.¹⁰ The collection site was cleaned with water and 70% alcohol to remove gross debris, bacteria, and saprophytic fungi such as *Alternaria* spp. Scaly material and hair were removed with a sterile hemostat from the periphery of the lesion. In some instances, direct microscopic examination of fresh hairs and skin scrapings in a 20% solution of potassium hydroxide in water or oil was performed; specimens were taken from areas suspected to be infected on newly admitted patients to identify hyphae and arthrospores before proceeding with fungal culture. Hairs that fluoresced under a Wood's lamp were collected. Alopecic areas were examined for stubby broken hairs, which were removed from the follicles. A brush was used to collect samples from animals in the posttreatment surveillance stage and from animals that were considered to have recovered from infection.

Specimens were inoculated on fresh dermatophyte culture medium, and plates were incubated at 33°C (91.4°F), protected against light and desiccation,¹¹ and examined daily. Fungi were identified microscopically by placing a portion of the colony on a glass slide and suspending it in sterile saline (0.9% NaCl) solution. In some instances, a strip of clear acetate tape was used to lift the colony. A drop of lactophenol blue stain was added to view the fungi.

Candida albicans was identified by inoculating serum or beef extract broth and incubating at 37°C (98.6°F) for 2 hours. The presence of a typical germ tube tail attached to the yeast cell was determined by use of a light microscope.¹²

Serum biochemical and hematologic tests^b were performed on 25 dogs (23 dogs with dermatophytosis and 2 dogs with dermatomycosis) and 10 cats (all with dermatophytosis) before treatment and during 3 successive months after treatment.

Treatment—For convenience of administration, kittens and cats that weighed < 2.6 kg (< 5.7 lb) received 1 tube of lufenuron paste (133 mg) administered orally. The smallest kitten weighed 0.5 kg (1.1 lb). Thus, dose range in this weight group was 51.2 to 266 mg/kg (23.3 to 120.9 mg/lb) of body weight. Cats that weighed between 2.6 kg (5.7 lb) and 5 kg (11 lb) were given 2 tubes (266 mg) of lufenuron; thus, dose range in this weight group was 53.2 to 102.3 mg/kg

(24.2 to 46.5 mg/lb). Cats that weighed > 5 kg (> 11 lb) received 3 tubes (399 mg) of lufenuron. The heaviest cat weighed 5.6 kg (12.3 lb); thus, dose in this weight group was 71.3 to 79.8 mg/kg (32.4 to 36.3 mg/lb).

Dogs received combinations of small, medium, and large lufenuron tablets (67.8 mg, 204.9 mg, and 409.8 mg, respectively). Dogs that weighed < 3.0 kg (6.6 lb) received 2 small tablets (135.6 mg of lufenuron). The smallest dog weighed 2.5 kg (5.5 lb); thus, dose range in this weight group was 46.8 to 54.2 mg/kg (21.3 to 24.7 mg/lb). Dogs that weighed 3 to 39 kg (6.6 to 85.8 lb) received from 1 medium to 5 large tablets; thus, dose in this weight group was approximately 52.5 to 68.3 mg/kg (23.9 to 31.1 mg/lb). Unless otherwise noted, all dogs and cats were treated once. For group comparisons, $P < 0.05$ was considered significant.

Results

Three hundred and fifty-seven dogs and cats met study criteria. Sixty animals were untreated controls, and 297 animals with fungal infections had been treated with lufenuron.

Control animals—Forty-two untreated control cats (19 males, 23 females) were included in the study; 1 cat was Siamese, and 41 were mixed-breed cats. Age ranged from 2 to 72 months (mean \pm SD, 11 \pm 14 months), and body weight ranged from 0.5 to 4.2 kg (1.1 to 9.2 lb; mean, 2.8 \pm 1.2 kg [6.2 \pm 2.6 lb]). All 18 control dogs (11 males, 7 females) were mixed-breed dogs; their ages ranged from 2 to 24 months (mean, 9.4 \pm 6.5 months), and they weighed from 2.3 to 30 kg (5.1 to 66 lb; mean, 9.4 \pm 6.5 kg [20.7 \pm 14.3 lb]). In 48 of the 60 dogs and cats, mycotic skin lesions were located on the head and neck; in 8 animals, lesions were located on the limbs and thorax; and in 4 animals, lesions were located on other parts of the body. All except 6 animals were infected with *M canis*; 3 cats and 1 dog were infected with *T mentagrophytes*, and 2 dogs were infected with *M gypseum*.

Clinical recovery without treatment occurred in 5 (8.3%) animals after 4 weeks, 3 (5%) animals after 4 to 6 weeks, and 50 (83.3%) animals after 12 weeks. Two cats remained infected longer than 5 months after initial evaluation. Mean recovery time of control dogs (109.5 \pm 30 days) was not significantly different from recovery time of control cats (94.7 \pm 22.9 days).

Dogs with dermatophytosis—One hundred and twenty-nine dogs (69 males, 60 females) were treated with lufenuron for dermatophytosis; 68 were mixed-breed dogs, 8 were Golden Retrievers, 7 were German Shepherds, 5 each were Boxers, Standard Poodles, and Pointers, and the remaining 31 dogs were of other breeds. Their ages ranged from 3 to 84 months (mean, 20.6 \pm 17.6 months), and body weight ranged from 2.5 to 39 kg (5.5 to 85.8 lb; mean, 20.0 \pm 9.5 kg [44.4 \pm 20.9 lb]). Forty-seven dogs were infected with *M gypseum*, 11 with *T mentagrophytes*, and 71 with *M canis*. Lesions were seen on the head and neck ($n = 108$), limbs (8), and trunk and back (11); 2 dogs had generalized infection.

Hair regrowth began in all treated dogs 10 or 11 days after treatment was begun, and complete clinical recovery was generally observed within 16 to 21 days after treatment. In 14 dogs from which samples for mycologic culture were obtained daily, mycologic cure (negative culture results) preceded clinical recovery by a mean of 6.25 days (mean, 14.5 ± 2.6 days vs 20.75 ± 4.2 days, respectively). Signs of healing were discernable even during the first week of treatment. In 1 dog, positive culture results were obtained again 25 days after treatment; the dog was treated with a second dose of lufenuron and responded well. In 6 dogs, clinical signs reappeared several weeks after the initial response to treatment; *M canis* was cultured from the lesions, and all dogs responded briskly to a second treatment.

Cats with dermatophytosis—One hundred fifty-nine cats had been treated with lufenuron for dermatophytosis; 71 were males, and 88 were females. One hundred forty-two of these cats were mixed-breeds, 8 were Siamese, 7 were Persians, 1 was an Angora, and 1 was a Himalayan. Ages ranged from 2 to 128 months (mean, 16.2 ± 16 months), and body weight ranged from 0.55 to 5 kg (1.2 to 11 lb; mean, 3.1 ± 1.1 kg [6.8 ± 2.4 lb]). One hundred fifty-six cats were infected with *M canis*, and 18 of these cats had generalized infection. Three cats were infected with *T mentagrophytes*. Lesions were located on the head and neck ($n = 136$), limbs (10), trunk (7), and tail (6).

In these treated cats, hair started to regrow after 5 or 6 days, and full growth was usually complete within 10 to 12 days. Mean clinical recovery time was 11.6 ± 1.4 days. Of the 18 cats with generalized *M canis* infection, 14 recovered within 10 days, 2 recovered within 11 days, and 1 recovered within 14 days. One 2-month-old Persian kitten did not recover, even after 20 days. Of the 23 cats examined individually on a daily basis by use of fungal culture, mycologic cure was detected within 7 to 14 days (mean, 8.3 ± 1.2 days), whereas clinical recovery was complete within 10 to 15 days (mean, 12 ± 1.8 days). In 1 cat, positive culture results were obtained again 35 days after treatment; a second treatment was administered, and negative culture results were obtained for the next 8 weeks. Three cats again developed clinical signs of infection several weeks after initial remission of clinical signs; *M canis* was cultured from the lesions, and the cats responded well to a second treatment with lufenuron.

Dogs with superficial dermatomycosis—Nine dogs (4 male, 5 female) were treated with lufenuron for superficial infections with various nondermatophytic fungi. Two dogs had disseminated *A niger* infection, 5 had cutaneous *A terreus* infection, and 2 had cutaneous *C albicans* infection. Six of these 9 dogs were mixed-breeds, 1 was a German Shepherd Dog, 1 was a Boxer, and 1 was a Golden Retriever. Mean body weight ranged from 11 to 33 kg ($[24.2$ to 72.6 lb; mean, 23.1 ± 7.6 kg [50.8 ± 16.7 lb]), and age ranged from 6 to 48 months (mean, 22 ± 13.8 months).

Lesions resolved between 17 and 34 days (mean, 21.2 ± 6.0 days) after treatment. In 2 dogs from which samples were obtained daily for fungal culture, myco-

logic cure was recorded on days 11 and 17, respectively, whereas clinical recovery was detected on days 18 and 29, respectively.

Effect of treatment on fungal characteristics—Microscopic observations on morphologic characteristics of cultured fungi were made in a culture taken from a cat 5 days after treatment with a dose of 71.4 mg of lufenuron/kg (32.5 mg/lb). The residual growth contained damaged and distorted macroconidia. In some instances, septa were missing, walls were crushed, and macroconidia were recognized only from the characteristic shape of the cell framework. In some colonies, intact macroconidia were evident and still able to grow.

Blood and serum biochemical analyses—Results of CBC and analyses of serum concentrations of albumin, BUN, calcium, cholesterol, creatinine, magnesium, ammonia, phosphorus, total bilirubin, total protein, triglycerides, glucose, and uric acid as well as serum activities of γ -glutamyltransferase, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, lipase, amylase, creatine kinase, and lactate dehydrogenase were within reference ranges before treatment and for 3 months after treatment.

Discussion

Results of the study reported here indicated that dermatophytosis persisted for 2 to 3 months in untreated animals, whereas dogs and cats that were treated with lufenuron had remission of clinical signs much more rapidly: approximately 10 to 15 days for cats and 16 to 25 days for dogs. Furthermore, mean recovery times of dogs affected by dermatophytosis and dogs affected by superficial dermatomycoses were quite similar.

Evaluation of results of daily mycologic culture of specimens from 16 treated dogs and 23 treated cats permitted a comparison of mycologic cure and clinical recovery times in these animals. In all instances, culture results were negative before clinical signs had disappeared. Differences in duration between these 2 findings ranged from 1 to 19 days for dogs and 1 to 5 days for cats.

Lufenuron appeared not to have adverse effects. Kittens that weighed as little as 0.5 kg received an entire tube (133 mg) of the drug, equivalent to a dose of 266 mg/kg, which is considerably larger than that typically administered for flea control,⁶ with no apparent adverse effects. Nevertheless, approximately 5% of treated animals became reinfected, including 1 dog and 1 cat that were monitored daily by use of fungal culture. Infections reappeared at 25 and 35 days after treatment, respectively, and were successfully treated with a second dose of lufenuron. It is not known whether these animals had become reinfected by natural exposure or were latently infected despite treatment. Nevertheless, oral administration of lufenuron appears to be effective for treatment of certain cutaneous fungal infections in dogs and cats.

⁶PROGRAM, Novartis, Basel, Switzerland.

⁷QBC VetAutoread Hematology System and VetTest Chemistry Analyzer, IDEXX Laboratories Inc, Me.

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A retrospective study was performed to evaluate use of lufenuron for treating cutaneous fungal infections in dogs and cats. Medical records of 156 dogs and 201 cats with dermatophytosis or superficial dermatomycoses were reviewed; 297 of these animals had been treated once by oral administration of lufenuron. Response to treatment was evaluated by use of fungal culture and evaluation of cutaneous lesions.

In treated dogs, mean durations from time of treatment to time of negative fungal culture results and resolution of gross lesions were 14.5 and 20.75 days, respectively. In all treated dogs, gross lesions resolved within approximately 21 days. In treated cats, mean durations from time of treatment to time of negative fungal culture results and resolution of gross lesions were 8.3 and 12 days, respectively. Time to resolution of lesions in most untreated control animals was approximately 90 days. Adverse effects of treatment were not detected. Results of this study suggest that lufenuron provides an effective, convenient, and rapid method for treating fungal infections in dogs and cats.—Y. Ben-Ziony and B. Arzi (*J Am Vet Med Assoc* 2000;217:1510-1513).