Influence of long-term treatment with tetracycline and niacinamide on antibody production in dogs with discoid lupus erythematosus

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Objective—To evaluate the effect of long-term treatment with tetracycline and niacinamide on antibody production in dogs by measuring postvaccinal serum concentrations of antibodies against canine parvovirus and canine distemper virus.

Animals—10 dogs receiving long-term treatment with tetracycline and niacinamide (treatment group) and 10 healthy dogs (control group).

Procedure—The treatment group included 9 dogs with discoid lupus erythematosus and 1 dog with pemphigus foliaceus on long-term treatment (> 12 months) with tetracycline and niacinamide. The control group included 10 healthy dogs with no clinical signs of disease and no administered medications for the past 3 months. Blood samples were obtained from all dogs by jugular venipuncture. Serum antibody titers against canine parvovirus and canine distemper virus antigens were measured, using hemaglutination inhibition and serum neutralization, respectively, and compared between groups.

Results—A significant difference in antibody titers between treatment- and control-group dogs was not found. All dogs had protective antibody titers against canine distemper virus, and 8 of 10 dogs from each group had protective titers against canine parvovirus infection.

Conclusion and Clinical Relevance—These results provide evidence that long-term treatment with tetracycline and niacinamide does not interfere with routine vaccinations and thus does not seem to influence antibody production in dogs. (*Am J Vet Res* 2002; 63:491–494)

Discoid lupus erythematosus (DLE) is one of the more common immune-mediated skin disorders in dogs. Initially, it is characterized clinically by depigmentation of the planum nasale and lips. As the disease progresses, erythema, erosions, ulceration, and severe crusting of the planum nasale and dorsal surface of the muzzle may develop. These lesions may also be observed periocularly or on the pinnae.[1,2] Classic treatment for DLE in dogs has often included immunosuppressive therapy with glucocorticoids, azathioprine, chlorambucil, or aurothioglucose used singly or in combination.[1,2] Immunosuppression predisposes patients to bacterial and fungal infections as well as generalized demodicosis.[3] Alternative treatments that are less likely to cause immunosuppression are also available. For milder forms of the disease, vitamin E supplementation has been advocated.[2] However, vitamin E may not be regularly effective.[4] Tetracycline alone[5-7] or in combination with niacinamide[8-10] has been reported to be an effective treatment of bullous pemphigoid and cicatricial pemphigoid in humans. Recently, this drug combination has been reported to be a safe treatment option for immune-mediated skin disorders such as DLE in dogs[11] and has also been of help in some dogs with sterile pyogranulomatous disease[12] and pemphigus foliaceus.[11]

Antibiotics are widely used for the treatment of bacterial infections in various species and may be able to influence the immune system in addition to their antimicrobial activity.[13,14] Tetracycline has been reported to affect antibody production in piglets and rabbits.[15,16] One of the possible effects of long-term use of tetracycline for treatment of DLE and pemphigus foliaceus in dogs may be suppression of antibody synthesis. This could interfere with routine vaccination against common and detrimental diseases such as distemper, hepatitis, parvovirus, and leptospirosis and thus increase susceptibility to these diseases. The purpose of the study reported here was to evaluate the effect of long-term treatment with tetracycline and niacinamide on antibody production in dogs by measuring postvaccinal serum concentrations of antibodies against canine parvovirus and canine distemper virus.

Materials and Methods

The treatment group in our study included 9 dogs with DLE and 1 dog with pemphigus foliaceus that were referred to the Veterinary Teaching Hospital at the Colorado State University. Diagnoses of DLE and pemphigus foliaceus were made on the basis of history, clinical signs, and dermatohistopathologic findings. Treatment-group dogs had received oral administration of tetracycline and niacinamide 1 to 3 times a day for at least 12 months. Dogs that weighed > 15 kg received 500 mg of each drug, and dogs that weighed ≤ 15 kg received 250 mg of each drug. Age, breed, sex, date, and vaccination history were obtained for all treatment-group dogs. The dose of tetracycline and niacinamide, concurrent medications, and observed adverse effects during treatment were recorded as well as clinical signs of infection as an indication for possible compromised cell-mediated immunity. The control group in our study consisted of 10 healthy dogs that were matched for age and sex with treatment-group dogs. Control

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dogs were admitted for routine booster vaccinations. Vaccination history was also recorded for control-group dogs.

From all dogs, blood was obtained by jugular venipuncture, spun, and frozen at –70 C. Serum was stored until batch testing. Serum was tested for antibody concentrations against canine distemper virus by serum neutralization and for antibody concentrations against canine parvovirus by hemaglutination inhibition. For evaluation of serum antibody titers against canine distemper virus in our laboratory, a titer of < 1:2 indicates a lack of immunity and susceptibility to infection, a titer of 1:2 to 1:16 indicates limited protection, and a titer > 1:16 indicates probable protective immunity. For evaluation of serum antibody titers against parvovirus in our laboratory, a titer of < 1:8 indicates a lack of immunity and susceptibility to infection, a titer of 1:16 to 1:32 indicates limited protection, and a titer of > 1:32 indicates probable immunity. At 3 months after revaccination of treatment-group dogs that had low antibody titers against parvovirus or distemper virus antigens, an attempt was made to reevaluate these dogs by obtaining an additional blood sample for antibody titer determination

Statistical analysis—Serum antibody titers against canine parvovirus and canine distemper virus antigens between treatment- and control-group dogs were compared individually, using a Wilcoxon rank sum test. A value of $P < 0.05$ was considered significant.

Results

The mean age of treatment-group dogs was 9.3 years with a range from 7 to 14 years. Six dogs were castrated males, 1 was a sexually intact male, and 3 were spayed females. All treatment-group dogs received tetracycline and niacinamide for > 12 months (mean, 34 months; range, 20 to 62 months) for DLE (9 dogs) or pemphigus foliaceus (1). The medication was given 3 times a day in 3 dogs, 2 times a day in 4 dogs, and once a day in the remaining 3 dogs.

In treatment-group dogs, the mean serum antibody titer against canine distemper virus antigen was 1:435 (range, 1:128 to 1:1,024), and the mean serum antibody titer against canine parvovirus antigen was 1:113 (range, 1:4 to 1:256). Three treatment-group dogs had serum concentrations of antibodies against canine parvovirus that indicated no protection (ie, titers of < 1:8) or limited protection (ie, titers of 1:16 to 1:32) against infection. Compared with the other treatment-group dogs, these 3 dogs were older (9, 11, and 14 years old); 2 of them received treatment once a day, and 1 dog received treatment 2 times a day. One of these 3 dogs was euthanized because of old age (ie, 14 years) before a second sample for serum antibody titer determination could be obtained. At 3 months after revaccination, 1 of the 3 dogs had serum antibody titers of 1:64 and 1:32 against canine parvovirus and canine distemper virus, respectively.

The control group consisted of 10 healthy dogs matched for age and sex with the treatment-group dogs. For control-group dogs, mean serum antibody titer against canine distemper virus antigen was 1:705 (range, 1:8 to 1:4,096) and against canine parvovirus antigen was 1:360 (range, 1:4 to 1:1,024). A significant difference in serum antibody titers against canine distemper virus or parvovirus between the 2 groups of dogs was not found ($P = 0.8$ for serum antibody titer against distemper virus antigen; $P = 0.058$ for serum antibody titer against parvovirus antigen).

Vaccination occurred between 4 and 60 months prior to obtaining blood samples in control-group dogs (mean, 26.9 months) and between 10 and 36 months prior to obtaining blood samples in the treatment-group dogs (mean, 17.1 months). Of the 10 control-group dogs, 2 were vaccinated ≤ 1 year prior to blood sample collection, 4 between 1 and 2 years prior to blood sample collection, and 4 > 2 years prior to blood sample collection. Of the 10 treatment-group dogs, 4 were vaccinated ≤ 1 year prior to blood sample collection, 4 between 1 and 2 years prior to blood sample collection, and 2 > 2 years prior to blood sample collection. Comparing the time elapsed between last vaccination and blood sample collection between groups did not reveal a significant difference ($P = 0.24$). The 3 dogs in the treatment group with low serum antibody titers received their last vaccination 7, 12, and 24 months prior to blood sample collection. In 2 control-group dogs with low serum antibody titers against parvovirus antigen and 1 control-group dog with a low titer against distemper antigen, 18, 36, and 24 months, respectively, had elapsed since vaccination. Two of the control-group dogs that were vaccinated 60 months prior to blood sample collection (all other dogs in this group were vaccinated within the last 36 months) had adequate serum antibody titers.

Six of the treatment-group dogs had no evidence of infections during the time of treatment. Two dogs received concurrent antibiotics at the beginning of treatment because of cytologic evidence of infection in the lesional skin. Both dogs had no further evidence of infection in the following 18 months of treatment. One dog had chronic allergies prior to the diagnosis of DLE and had recurrent anal sacculitis. The latter required intermittent antibiotic treatment until removal of the anal sacs. For the following 2 years, the dog was treated without any evidence of infection. One dog had concurrent hypothyroidism and had otitis externa and pyoderma 5, 10, and 16 months and bacterial cystitis 30 months after beginning treatment with tetracycline and niacinamide.

Discussion

Discoid lupus erythematosus and pemphigus foliaceus are more common immune-mediated skin diseases regularly seen in small animal practice.[17,18] Until recently, immunosuppressive therapy with glucocorticoids or cytotoxic agents was commonly used.[1,2] Glucocorticoids are associated with numerous adverse effects similar to the clinical signs observed in idiopathic hyperadrenocorticism and ranging from polyuria/polydipsia and polyphagia (in most patients), lethargy, muscle loss, exercise intolerance, secondary infections particularly of the lung, skin, and urinary tract to severe skin changes such as calcinosis cutis.[19] Cytotoxic agents such as azathioprine share the potential for teratogenicity and bone marrow suppression and thus the need for regular CBC to avoid possibly fatal thrombocytopenia, leukocytopenia, or anemia.[2,20] Azathioprine may also be severely and acutely hepatotoxic in some dogs and cats.[3]

Proposed alternative treatments for DLE in dogs include essential fatty acid supplementation,[21] vitamin E,[2] and more recently a combination of tetracycline and niacinamide.[11] In a study[12] evaluating treatment with tetracycline and niacinamide for DLE in 20 dogs, 14 (70%) responded well and did not need to undergo classic immunosuppression. However, of 8 dogs with pemphigus foliaceus included in that study, only 1 had a good response. The only adverse effects seen in the study by White et al[11] were lethargy and anorexia in 4 dogs (which resolved when niacinamide was administered only 1 or 2 times a day instead of 3 times a day) and diarrhea in 1 dog. Two of the dogs included in our study had vomiting as an adverse effect. In 1 of these dogs vomiting only occurred when the drugs where not given with food. The other dog vomited only occasionally, and a change of dose or drugs was not necessary.

Tetracycline has several effects on the immune system. Chemotaxis of human polymorphonuclear neutrophils was inhibited in vitro.[22,23] Suppression of phagocytosis was reported in humans[24] and cattle.[25] In mice, tetracycline suppressed IL-1 secretion of stimulated thymocytes.[26] Tetracycline had a negative effect on lymphocyte proliferation.[27,28] Antibody production in mice was suppressed in vitro[29] but not in vivo.[30] In piglets and rabbits, oxytetracycline suppressed antibody production in response to inactivated salmonellosis vaccine.[16] Reduced immunity of piglets to a challenge with virulent *Salmonella* strains was reported when tetracycline was given before vaccination.[15] After concurrent tetracycline administration and vaccination with *Yersinia ruckeri* O-antigen bacterin, decreased numbers of antibody-producing cells were detected in salmon.[31]

Routine vaccination for dogs at our veterinary teaching hospital includes modified-life canine parvovirus, parainfluenza virus, distemper virus, and adenovirus strains. Of these, vaccination with distemper virus and parvovirus induces a strong and long-lasting antibody response.[32] A high antibody titer in any dog vaccinated within the last 12 months is expected in most dogs irrespective of exact date of vaccination.[33] Thus, antibody titers against distemper virus and parvovirus in dogs vaccinated regularly for these diseases are useful markers for antibody production in general. However, in a recent study[34] it was shown that serum antibody titers against canine parvovirus antigen were low in a small percentage of vaccinated dogs. This percentage increased in older dogs.[34] In our study, all treatment-group dogs had protective serum antibody titers against canine distemper virus antigen, and most (7/10) dogs had protective serum antibody titers against canine parvovirus antigen. Most (8/10) dogs were older than 8 years of age, and all 3 treatment-group dogs with low serum antibody titers against parvovirus antigen were in this age group. In 19 clinically normal dogs > 8 years of age, 6 dogs had serum antibody titer ≤ 1:10, and an additional 2 dogs had serum antibody titers of 1:20 against parvovirus.[34] Two of the 3 treatment-group dogs in our study with low serum antibody titers against parvovirus received treatment only once a day. Assuming the effects of treatment are dose-related, this would make a drug effect on antibody titers less likely. The fact that 1 of these dogs had protective serum antibody titers to both antigens when reevaluated 3 months after revaccination would also argue against an effect of these drugs on immune response. A significant difference in antibody response between treatment- and control-group dogs was not found. The time elapsed from last vaccination to sample collection could affect serum antibody titers. However, there was a great variation of time since last vaccination in dogs with low or high serum antibody titers in both groups, suggesting that the lack of a difference between groups is not the result of a time factor. Further support for this statement is that a significant difference in the time span from last vaccination to blood sample collection between groups was not found.

These results suggest that long-term treatment with tetracycline and niacinamide does not seem to interfere with an immune response to routine vaccinations and is unlikely to influence antibody production in dogs. However, because of the small sample size, minor changes may have escaped detection. A negative influence on cell-mediated immunity also seems unlikely, as only 2 dogs had evidence of infection during long-term treatment, and concurrent diseases explaining these infections were determined for both dogs.

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