Paper

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Efficacy of dimetinden and hydroxyzine/chlorpheniramine in atopic dogs: a randomised, controlled, double-blinded trial

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Antihistaminic drugs are commonly used as symptomatic therapy of atopic dermatitis in dogs. Unfortunately, their clinical benefit is largely unsubstantiated. In a double-blinded, placebo-controlled, cross-over trial, the influence of dimetinden and of a combination of chlorpheniramine and hydroxyzine on pruritus and lesions was evaluated in 19 dogs. They were treated with either product or a placebo orally for 14 days, each time followed by a 14-day washout period. Before and after each period, the dogs were examined and the Canine Atopic Dermatitis Extent and Severity Index (CADESI) determined by a clinician, and the pruritus and general condition by the owner. Dimetinden improved the pruritus significantly (P=0.014) but not the CADESI (P=0.087), the combination of hydroxyzine and chlorpheniramine improved the CADESI (P=0.049) and pruritus (P=0.05) significantly. Ten of 17 dogs improved by more than 25 per cent in pruritus with the combination of hydroxyzine and chlorpheniramine, 12 of 18 with dimetindenmaleate and only 2 of 19 with placebo. Antihistamines can help to reduce pruritus in atopic dogs, but in most cases, the improvement is limited and additional treatment may be needed.

Introduction

Canine atopic dermatitis is a common skin disease in small-animal practice (Scott and Paradis 1990). It is a genetically predisposed, pruritic skin disorder with a hypersensitivity against environmental and/or food allergens (Olivry and others 2001, 2007a). Allergen-specific IgE molecules are bound to high-affinity FcEpsilonR1-receptors on canine mast cells (Hill and Martin 1998). Upon crosslinking of two IgE antibodies by an allergen, mast cell degranulation will lead to a release of various cytokines and inflammatory mediators such as histamine (Schwartz 1994, Hill and Martin 1998, Hill and Olivry 2001). Histamine binds to histamine-1-receptors in the skin, and induces immediate and late-phase allergic reactions of canine atopic dermatitis (Bachert 1998, DeBoer and Griffin 2001, Simons 2004) leading to pruritus, frequently in the interdigital, inguinal and perianal area, axillae and on the head (Griffin and DeBoer 2001).

The only specific treatment for atopic dermatitis is allergen-specific immunotherapy (Mueller and Bettenay 1996, Olivry and Sousa 2001a, Loewenstein and Mueller 2009). Symptomatic treatment includes a number of options, such as glucocorticoids (Olivry and Sousa 2001b), cyclosporine (Steffan and others 2006), shampoos (Löflath and others 2007), essential fatty acids (Mueller and others 2004, Olivry and others 2010a, b) and antihistamines (DeBoer and Griffin 2001, Olivry and Mueller 2003). Antihistamines act as inverse agonists on histamine receptors, they stabilise the negative conformation of the receptor, and signal transduction ceases (Leurs and others 2002, Simons 2004). They are often used in human and veterinary medicine (Hoare and others 2000, DeBoer and Griffin 2001, Olivry and Mueller 2003). However, a systematic review of treatments for canine atopic dermatitis did not provide conclusive evidence for the efficacy of antihistamines (Olivry and others 2010b).

As a consequence, recent practice guidelines for treatment of canine atopic dermatitis do not recommend antihistamines for the treatment of active atopic dermatitis and state, that it is unclear if dogs with mild disease would benefit from treatment with that class of drugs (Olivry and others 2010a). The aim of this study was to evaluate the influence of the two antihistamines, dimetinden (Fenistil, Novartis) and hydroxyzine/chlorpheniramine (Histacalmine, Virbac) on canine atopic dermatitis in a double-blinded, placebo-controlled, cross-over study.

Material and methods

Study population

Dogs diagnosed with atopic dermatitis by history, clinical examination and ruling out other differential diagnoses, such as food adverse reaction, flea allergy dermatitis or scabies by appropriate tests and treatments as reported (DeBoer and Hillier 2001, Hillier and Griffin 2001) were included in this study. Prior to inclusion, secondary skin infections with bacteria or yeast organisms were ruled out by clinical examination and impression smears.

Glucocorticoids and cyclosporine had to be withdrawn four and six weeks, respectively, prior to inclusion. Similarly, other antihistamines were not permitted and had to be discontinued at least 14 days before the trial. Additional symptomatic therapy, such as shampoos, essential fatty acids or flea control, that was begun more than three months prior to inclusion was permitted and continued unchanged during the trial. Allergen-specific immunotherapy was also permitted if it was begun at least one year prior to inclusion, and dose and frequency of allergen

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injections were not changed during the trial. Diet changes were not permitted for at least eight weeks prior to inclusion and during the trial.

Study design

The study was conducted as a randomised, placebo-controlled, double-blinded, cross-over trial. Prior to inclusion, all owners signed an informed consent form. A formal approval of governmental authorities was not needed for this study. Dogs were assigned to the two treatment groups and the placebo group in a randomly chosen order. Neither owner nor evaluating clinicians were aware of the sequence of medications which were dispensed in identical vials without any product information besides the number of tablets to be given and the frequency of dosing which was identical in all groups. Before and after each medicated period dogs underwent a clinical and dermatological examination. A washout period of two weeks was undertaken between the three different treatment courses.

Study intervention

Each dog received placebo and medications for a 14-day period. The dosage used was 1 tablet per 10 kg of bodyweight administered twice daily, which equalled a total daily dose of 1 mg dimetindenmaleate (Fenistil, Novartis)/10 kg bodyweight and 0.7 mg chlorpheniramine and 20.9 mg hydroxyzine (Histacalmine, Virbac)/10 kg. The coated tablets were not divided in half. The tablet doses for different bodyweights are listed in Table 1.

Assessment of treatment efficacy

At each clinical examination, the clinician determined a validated lesion score (Canine Atopic Dermatitis Extent And Severity Index, CADESI). This score evaluates erythema, alopecia, lichenification and excoriation on 62 areas of the body on a scale from zero to five (Olivry and others 2007b). The owners rated the current pruritus on the day of consultation on a visual score from 0 (no pruritus visible) to 10 (severe pruritus), using a validated pruritus scale (Hill and others 2007, Rybnicek and others 2009). Furthermore, owners rated the overall condition before and after treatment as improved, deteriorated or unchanged. As only limited improvement was expected with antihistamine treatment (compared with cyclosporine or glucocorticoids), the number of dogs improving by more than 25 per cent and 50 per cent, respectively, in each group, was determined as well. Additionally, it was determined how many dogs improved, stayed the same or deteriorated in the washout phase.

Statistical evaluation

The improvement or deterioration of pruritus and CADESI scores was calculated for each dog by subtracting the score obtained prior to medication from the score after two weeks of treatment. The changes in pruritus and CADESI seen with each medication were compared with those seen with placebo using a Mann-Whitney U Test. Additionally, the number of dogs improving by more than 25 per cent and 50 per cent was determined for each group, and compared with a Fisher's exact test. Prism V.5.0 software was used for the calculations (Prism, Graphpad, San Diego, USA). A one-sided P value of ≤0.05 was determined significant, as it was considered unlikely that treatment could lead to deterioration of clinical signs of CAD compared with placebo.

Results

Study population

Twenty dogs were included in this study and 19 dogs completed the trial. One dog was excluded due to compliance problems. The remaining 19 dogs consisted of 11 male and 8 female dogs with a mean age of 4.9 years (range 12 months to 11 years). There were seven mongrels and 12 purebred dogs from 10 different breeds. All dogs showed moderate to severe pruritus at presentation. Eleven dogs were exclusively allergic to environmental allergens, eight dogs had improved partially on an elimination diet prior to inclusion and received a special diet for that reason. Ten dogs showed pruritus all year, but deteriorated seasonally; the study took place during the individual pruritic season of the dogs. Nine dogs showed equal pruritus all year round. The age of disease onset was between six months and four years. The dogs' mean bodyweight was 17.2 kg (range 6.8–32 kg).

TABLE 1: Tablets administered to dogs in the study evaluating the combination of chlorpheniramine and hydroxyzine, dimetinden and placebo, respectively

Bodyweight (kg)	Tablets administered
0–9.9	1 once daily
10–19.9	1 twice daily
20–29.9	2 in the morning, 1 in the evening
30–39.9	2 twice daily
40–49.9	3 in the morning, 2 in the evening

Assessment of treatment efficacy

Only two dogs received dimetinden and placebo, and only one dog placebo and the combination of chlorpheniramine and hydroxyzine; then the owners opted to discontinue the study due to insufficient improvement. Thus, 17 dogs received the combination of chlorpheniramine and hydroxyzine, 18 dogs dimetinden and 19 dogs placebo. Descriptive statistics of pruritus and CADESI before and after each medication are listed in Table 2, raw data is listed in Table 3. When comparing changes during treatment, there was a significant difference in pruritus between placebo and dimetinden (P=0.014) and hydroxyzine/chlorpheniramine (P=0.05), respectively, and between placebo and the combination of chlorpheniramine and hydroxyzine in CADESI (P=0.049). This difference was not significant in regard to CADESI for dimetinden (P=0.087). Mean CADESI scores improved by 47 per cent after the treatment with hydroxyzine/chlorpheniramine and 38 per cent after dimetinden. They deteriorated by 12 per cent when dogs were treated with placebo. Improvement of more than 25 per cent (50 per cent) of pruritus was seen in 10 (2)/17 dogs with the combination of chlorpheniramine and hydroxyzine, 12 (2)/18 with dimetinden and 2 (1)/19 with placebo. For dogs improving by more than 25 per cent, the difference between placebo and the combination of chlorpheniramine and hydroxyzine and dimetinden, respectively, was significant (P=0.003 and P=0.001, respectively). The mean improvement was 24.7 per cent with chlorpheniramine/hydroxyzine and 22.1 per cent with dimetinden, mean pruritus scores did not change in the placebo group. Three dogs improved only with the combination of chlorpheniramine and hydroxyzine, five dogs only with dimetinden and nine dogs with both medications. In two dogs, there was no improvement seen with either one of the medications. For CADESI, the corresponding figures were 11 (6)/17 dogs with the combination of chlorpheniramine and hydroxyzine, 7 (3)/18 with dimetinden and 5 (1)/19 with placebo. For dogs improving by more than 25 per cent, only the difference between placebo and the combination of chlorpheniramine and hydroxyzine was significant (P=0.023). Of the 19 dogs, 16 underwent two washout phases, 3 dogs dropped out of the study after the second medication phase (always after being treated with placebo) and, thus, there were 35 washout phases to evaluate. Twenty-three dogs got worse in the washout phase regarding CADESI and pruritus, 10 stayed the same with regard to

TABLE 2: Descriptive statistics of pruritus and CADESI of dogs before and after individual medications

	Mean±SD	Range	Median	95% CI
Combination of chlorpheniramine and hydroxyzine				
Pruritus at day 0	7.2±1.4	5–10	7	6.5 to 8.0
Pruritus at day 14	5.4±1.9	2–9	6	4.4 to 6.4
CADESI at day 0	32±36	3–140	17	13 to 51
CADESI at day 14	17±21	1–67	8	7 to 28
Dimetinden				
Pruritus at day 0	6.9±1.9	4–10	6.5	5.9 to 7.8
Pruritus at day 14	5.2±1.8	2–8	6.0	4.3 to 6.1
CADESI at day 0	34±50	3–211	16	9 to 59
CADESI at day 14	21±18	2–63	14	12 to 30
Placebo				
Pruritus at day 0	6.4±1.3	4–8	6	5.7 to 7.1
Pruritus at day 14	6.4±1.8	2–9	6.5	5.5 to 7.2
CADESI at day 0	26±35	2–124	11.5	9 to 44
CADESI at day 14	29±35	3–122	16.5	12 to 47

CADESI, Canine Atopic Disease Extent and Severity Index

TABLE 3: Raw data of the dogs treated with dimetinden, hydroxyzine/chlorpheniramine or placebo

No.	Sequence	H Pru 1	H Pru 2	H CAD 1	H CAD 2	D Pru 1	D Pru 2	D CAD 1	D CAD 2	P Pru 1	P Pru2	P CAD 1	P CAD 2
1	DPH	7	5	68	66	6	2	40	25	6	6	45	44
2	DPH	6	6	5	5	4	2	4	4	4	2	4	5
3	PHD	10	2	67	16	6	8	75	55	6	8	35	42
4	PHD	6	6	13	2	6	6	8	12	6	5	5	37
5	DP					8	6	211	63	8	9	110	122
6	HP	6	3	3	2					6	8	4	3
7	HPD	8	6	15	1	7	4	11	10	8	7	12	8
8	DPH	8	5	140	23	9	7	85	43	8	7	124	113
9	PDH	6	4	9	8	4	6	8	8	6	6	2	4
10	DP					8	6	21	15	8	8	7	43
11	DPH	6	4	28	6	10	6	7	13	6	8	11	15
12	PDH	6	6	17	22	6	4	8	12	5	6	14	18
13	PHD	8	8	4	3	8	8	3	5	6	8	3	4
14	HDP	9	9	23	33	7	5	34	36	8	4	28	13
15	PDH	9	8	75	67	10	6	42	21	8	7	33	21
16	DHP	8	7	29	20	9	6	26	21	8	8	56	46
17	HPD	5	3	4	3	4	3	3	3	4	4	4	3
18	PDH	8	6	38	13	6	5	28	25	6	6	24	28
19	DPH	7	4	8	3	6	4	6	2	6	6	8	7

CAD, Canine Atopic Extent and Severity Index; D, Dimetinden; H, Hydroxyzine/chlorpheniramine; P, Placebo; Pru, Pruritus, 1, Score before treatment; 2, Score after 2 weeks of treatment

their pruritus and 7 with regard to their CADESI (6 and 4 dogs, respectively, had received placebo in the preceding medication phase) and 2 and 5 improved, respectively. Changes in overall condition are shown in Table 4.

Adverse effects

Clinical adverse effects were observed in two dogs with dimetinden, and four dogs with the combination of chlorpheniramine and hydroxyzine. All these dogs showed drowsiness during drug administration. In one dog with a BW of 23 kg the dimetinden dosage had to be reduced from three tablets daily to two tablets daily after five days of drug intake. With that adjustment the drowsiness resolved, and the activity level went back to normal. The pruritus improved, nonetheless, from 7 to 4. In all other dogs the dose did not have to be changed, because the drowsiness was only very mild.

Discussion

Atopic dermatitis is a common disease in small-animal practice (Lund and others 1999). Avoidance of offending allergens is often not possible in this disease. Allergen-specific immunotherapy takes months to optimal effect (Mueller and Bettenay 1996), and in many cases will still require additional symptomatic therapy (Loewenstein and Mueller 2009). As atopic dermatitis typically requires life-long management, treatments with infrequent and mild clinical adverse effects are preferred. Antihistamine pharmacotherapy blocking the signal transduction induced by histamine released by mast cells after cross-linking of IgE-molecules on their surface has been reported to be beneficial for dogs with atopic dermatitis (Bachert 1998, DeBoer and Griffin 2001, Simons 2004). There is not much reliable information about the use of a combination of chlorpheniramine and hydroxyzine in dogs, and to the authors' knowledge, dimetinden has not been evaluated in dogs as yet. In human medicine, dimetinden is used as efficacious treatment for atopy for more than 40 years (Kuokkanen 1975, Behrendt and Ring 1990). This study provides evidence for a mild clinical improvement of CAD with a combination of chlorpheniramine and hydroxyzine and with dimetinden over and above what is seen with placebo treatment.

The benefits of dimetinden and chlorpheniramine/hydroxyzine in this study varied from dog to dog. Although not every dog responded to antihistamine treatment, most dogs in this study did to different degrees. Approximately two-thirds of the dogs improved in pruritus by more than 25 per cent with either of the antihistaminic medications. Improvement of lesions was more frequently seen with the combination of chlorpheniramine and hydroxyzine. However, there was no difference between the treatment groups and the placebo group when evaluating dogs improving by more than 50 per cent in lesions or pruritus. This corresponds to anecdotal reports stating a consistent but mild effect of antihistamines on CAD. They are rarely suited as sole therapy in dogs with AD, but rather can be used as supporting agents combined with other treatment options (Mueller and Jackson 2012, Marsella 2013). They may also be useful to maintain remission in dogs previously treated with more potent anti-inflammatory drugs.

However, the efficacy of antihistamines cannot be compared to glucocorticoids and cyclosporine, thus they are not suitable to treat an acute flare of a severly atopic dog where a fast and reliable decrease in pruritus is desired to improve the dog's (and owner's) quality of life and minimise the chance of secondary infection.

As some of the dogs in this study had clinical signs that were worse seasonally, some of the improvement seen may have been due to a change of season. However, great care was taken to test each dog completely within their peak allergy season based on their history. Additionally, in two-thirds of the washout periods, a deterioration of clinical signs was seen, in some others the pruritus and CADESI did not change, and only in very few dog was an improvement seen within a washout period. Thus, it seems unlikely that seasonal changes contributed to a relevant degree to the results of this study.

Most dogs had mild atopic dermatitis based on the CADESI severity scale (Olivry and others 2007b), two had severe atopic dermatitis and three moderate atopic dermatitis. The lesion scores of both severely affected dogs responded well to antihistaminic treatment, all the moderately affected dogs showed some lesional improvement with one of the antihistamines, while none of those dogs improved with placebo. The small number of dogs precludes any statistical analysis of this subgroup. However, it seems that antihistamines do have some effect in more severely affected dogs, and randomised studies evaluating their use in this subgroup are indicated.

Of the dogs which participated in all three medicated periods, there were only two that did not respond to either one of the drugs. Most dogs responded to both medications, some only to one of the two. This confirms previous recommendations that several subsequent trials of different antihistamines may be sensible in individual patients (DeBoer and Griffin 2001).

In this study, clinical side effects were only reported in a few dogs. Only in one dog, sedation resulted in adjustment of the medication dose, in the other dogs showing sedation, it was so mild that no dose adjustment was required. The dog receiving a decreased dose still responded clinically, possibly increased drug concentrations due to

TABLE 4: Mean Percentage of dogs that showed improvement, deterioration or no change in overall condition

	Improvement	Deterioration	No change
Combination of chlorpheniramine and hydroxyzine	47	5.9	47.1
Dimetinden	50	11.1	38.9
Placebo	11.1	22.2	66.7

increased absorption or decreased metabolisation were responsible for adverse effects and, thus, a dose decrease was not associated with a lack of response.

In summary, this study provided evidence for mild improvement of canine atopic dermatitis treated with dimetinden and with a combination of chlorpheniramine and hydroxyzine. Furthermore, some dogs responded to both, some to one, and some to the other of the drugs, providing evidence for subsequent trials with different antihistamines in individual atopic dogs.

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