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Effects of cetirizine in dogs with chronic atopic dermatitis: a randomized, double blind, placebo-controlled trial

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This study was conducted to evaluate the effects of cetirizine in dogs with atopic dermatitis (AD) while fulfilling Favrot's diagnostic clinical criteria. Dogs received either 3 mg/kg cetirizine (n = 27), or a placebo (n = 23) orally once daily for 14 days in a randomized, double blind, placebo-controlled study, without concomitant medication. The effects were evaluated using a pruritus visual analog scale at the start (day 0) and at day 14. After 14 days, cetirizine clearly had no effect on the pruritus in dogs with chronic AD, and there was no significant difference between groups. These findings indicated that cetirizine (and likely H1 histamine receptor antagonists in general) should not be recommended for the control of pruritus in dogs with long term allergies.

Keywords: atopic dermatitis, cetirizine, dogs, placebo-controlled study

Introduction

Most skin disorders in dogs are accompanied by pruritus of various degree and origin. Allergies are preceded only by parasitic diseases, yeast and fungal infections in importance. Indeed, approximately 10 to 15% of the canine population is affected by atopic dermatitis (AD). Atopic dermatitis is a multifactorial disorder with a genetic predisposition and characteristic clinical features associated with environmental allergens. Clinical diagnoses of AD are primarily based on disease history and the clinical signs, which commonly include the presence of pruritus on the muzzle, lips, pinnae and/or the feet. In addition, the occurrence in a predisposed breed and the onset at young age enhance the possibility of AD [7,9,15,23]. Interestingly, evidence suggests that dogs also have a predisposition to develop clinical signs compatible with AD triggered by food antigens [15,20]. Therefore, certain dogs with food-induced AD (FIAD) and non-food-induced AD (NFIAD) cannot be differentiated on a clinical basis. Favrot *et al.* [6] recently conducted a validation study of the characteristic symptoms and signs related to canine AD [6], which led to adaptation of the existing list of criteria for the clinical diagnosis of cAD [24]. These so-called Favrot's criteria [6] are now commonly used to identify atopic conditions in dogs caused by food-induced and/or environmental allergens (Table 1).

Systemic treatments to control the symptoms of pruritic dermatoses include the use of glucocorticoids, ciclosporin A, H1 antagonist-type antihistamines, and oclacitinib [4,14]. In Asian countries, antihistamines are commonly the first choice to control pruritus in response to allergy. However, their efficacy is controversial. For example, the International Task Force on Canine Atopic Dermatitis (ITFCAD) does not recommend for or against its use because of a lack of sufficient

Table 1. Favrot's 2010 criteria for canine atopic dermatitis

1. Onset of signs under 3 years of age
2. Dog living mostly indoors
3. Glucocorticoid-responsive pruritus
4. Pruritus sine materia at onset (i.e. nonlesional pruritus)
5. Affected front feet
6. Affected ear pinnae
7. Non-affected ear margins
8. Non-affected dorsolumbar area

A combination of five satisfied criteria has a sensitivity of 85% and a specificity of 79% to differentiate dogs with atopic dermatitis (AD) from those with chronic or recurrent pruritus without AD.

controlled studies and inappropriate doses [3,16]. These studies are also lacking for other cutaneous pruritic disorders such as flea bite hypersensitivity, food-induced AD, and other manifestations of cutaneous adverse food reactions [11,12,19]. If clinicians still want to use type 1 antihistamines, it is recommended that their use be restricted to antihistamines with confirmed inhibitory effects on intradermal histamine injections [13], such as hydroxyzine [1] or its metabolite, cetirizine (0.5−1.0 mg/kg daily) [2,5,22]. Therefore, this study was conducted to evaluate the effects of cetirizine in a double-blind, placebo-controlled clinical trial in dogs with pruritus associated with non-food- or food-induced AD.

Materials and Methods

All dogs entered the trial with the owners' informed consent in writing. The study had a randomized, double-blind, placebo-controlled design.

Inclusion criteria

Client-owned dogs with pruritus for at least 6 months and a pruritus degree of 3 or more at inclusion (on a scale of 0: healthy dog, itching no problem; 3: mild itching, no itch when sleeping, playing or distracted; 10: extremely severe itch, almost continuous, cannot be distracted) were allowed to participate [8,21].

Prior to inclusion, all dogs were withdrawn from anti-inflammatory or anti-pruritic medications. This period was at least 14 days for topical glucocorticoids, oral glucocorticoids, and antihistamines, and at least 4 weeks for long-acting corticosteroids [18,21]. During the withdrawal period, dogs were treated with 3% chlorhexidine shampoo (Douxo; Sogeval Laboratories, France; 1−2 times weekly) to prevent development of secondary infections. All dogs were on a flea control treatment with fipronil spot-on (Frontline; Merial, France) for at least 3 months before inclusion, and this was continued during the trial. No other medication was provided.

All dogs underwent a general physical and dermatological examination. In addition, they were subjected to multiple skin scrapings, Woods' light examination, hair plucking, and impression smear collection to identify bacterial, parasitic and fungal diseases. Dermatophyte Test Medium was used to culture potential dermatophytes (BBL Mycosel Agar; Becton, Dickinson and Company, USA) and impression smears were subjected to Diff-Quick stain (Diff-Quik; Laboklin, Germany). If the dogs fulfilled Favrot's diagnostic criteria for atopic dermatitis [6], a clinical diagnosis of AD (non-food-induced and/or food-induced) was made. If allowed, dogs underwent a dietary challenge test of at least 6 weeks using a home-cooked novel protein diet (ostrich and rice, potatoes or yams) or a commercially-available, hydrolyzed protein diet (Hill's Prescription Diet z/d, Hill's Pet Nutrition; USA; Royal Canin Hypoallergenic DR21; Royal Canin, USA). Dogs with at least

90% reduction of pruritus in response to such dietary challenge were categorized as having food-induced AD (FIAD). Dogs with less than 40% improvement were classified as having non-food induced AD (NFIAD). NFIAD/FIAD dogs met the Favrot's criteria, but had a partial response (40−90%) to the dietary trial; therefore, they were considered to have a combination of a nonfood-induced AD (NFIAD) and a food-induced AD (FIAD). If a dog owner did not wish to subject the animal to a dietary trial, but the dog met the Favrot's criteria, a diagnosis of undetermined AD (UAD) was made [6].

Exclusion criteria

Dogs with parasitic or fungal disorders or flea bite hypersensitivity were not included in the study. In addition, dogs were withdrawn from the study if anti-inflammatory or anti-pruritic drugs other than the study drug were administered during the trial period, and if owners failed to comply with the study protocol.

Treatment groups

Dogs were randomly allocated to two treatment groups, those receiving cetirizine dihydrochloride (Taiwan Biotech, Taiwan) at 3 mg/kg/day and those receiving a placebo of corn starch. Treatments were administered for 14 days. Study medication or placebo was supplied as identical, nontransparent, encoded capsules of 10 mg. Throughout the study, the same batch of antihistamine or placebo capsules was used. Computerized randomization lists were made by the pharmacist at Taipei Medical University Pharmacy and kept away from the clinic. The study was blinded to both the investigators and the dog owners. Treatment groups were decoded after analysis of the data.

Evaluation and follow-up

At the start of the trial (day 0) and after 14 days (day 14) of treatment with either cetirizine or the placebo, a full physical and dermatological examination was performed. The dog owners were instructed about the use of the validated pruritus visual analog scale (VAS) [21] to report the severity of pruritus at day 0 and day 14. Adverse events were also recorded.

Statistical analysis

Efficacy data were analyzed using the Prism 6.0 (GraphPad Software, USA) software. Dogs that completed the study were included in analysis of the VAS pruritus scores. The mean VAS scores at day 0 were compared with those after 14 days of treatment (day 14). The cetirizine-treated group and the placebo-treated group were compared using the Mann-Whitney U test. A two-tailed p value < 0.05 was considered to be statistically significant. A 'per protocol' analysis was conducted alongside an 'intention-to-treat' analysis, if relevant.

Results

A total of 57 dogs met the inclusion criteria. Seven dogs did not complete the study as the pet owners wanted additional antipruritic medication (n = 6) or because the dog experienced drowsiness (n = 1). The male/female ratio, age at presentation and duration of the pruritus of the 50 dogs that completed the trial are given in Table 2. No significant differences in these data were observed among the 57 dogs.

The study population consisted of a large variety of breeds, including Dachshunds, Poodles, Beagles, French Bulldogs, Shih Tzus, and mixed breeds representing 77.7% in the cetirizine group (n = 27) and 52.2% in placebo-treated (n = 23) group.

Within the total group of 50 dogs fulfilling the inclusion criteria, 21 dogs had non-food-induced AD (NFIAD), four had food-induced AD (FIAD), five had a combination of NFIAD and FIAD, and 20 had undetermined AD (UAD) (Table 3).

The pruritus VAS scores were not significantly different between groups ($p > 0.05$; Table 2), nor between subgroups NFAID and UAD (Table 3), when the effect of cetirizine and placebo treatment were compared. The FIAD and the combined NFIAD/FIAD group were not evaluated by statistical analyses due to their small sizes. As shown in Fig. 1, the individual changes in pruritus VAS scores of the dogs before and after treatment showed a similar distribution and deterioration in both groups.

Discussion

Our double blind, placebo-controlled trial clearly demonstrated that cetirizine has no superior effect over placebo. This occurred when the entire placebo-treated and cetirizine-treated group was compared, as well as when the control group was compared with the subgroups of AD. According to the 2015 updated guidelines of the International Committee on Allergic Diseases of Animals (ICADA), modest efficacy against pruritus in general, either alone or in combination with each other, is expected for oral antihistamines, but their effects appear to be vary between individuals [14]. Considering that the pruritic skin problems in our dogs were of a chronic nature, our results are in line with the preliminary recommendations of ICADA
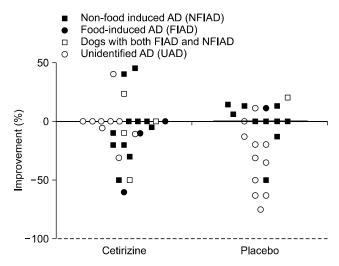
Table 2. Baseline characteristics of the study population

Variable	Cetirizine group (n = 27)	Placebo group (n = 23)
M/F ratio	14/13	7/16
Age at presentation (range, yr)	5.0 (0.5–12.0)	6.0 (1.5–11.5)
Duration of pruritus (range, yr)	2.0 (0.5–11.0)	3.0 (0.5–9.5)
VAS D0* (median and range)	7.0 (4–10)	8.0 (3–10)
VAS D14† (median and range)	7.0 (2–10)	7.0 (2–10)

M, male; F, female; VAS, visual analog scale. *At the start of the trial (day 0). †At the end of the trial (day 14).

Fig. 1. Individual and median group improvement (%) of dogs with atopic dermatitis treated with cetirizine (n = 27) or a placebo (n = 23).

Table 3. Composition and visual analog scale pruritus scores of the study population

Groups	Cetirizine group (n = 27)			Placebo group (n = 23)		
	Number of dog (n)	VAS D0	VAS D14	Number of dog (n)	VAS D0	VAS D14
NFIAD	11	7.0 (4–10)	7.0 (2–9)	10	8.0 (3–10)	8.3 (3–10)
FIAD	3	8.0 (5–10)	8.0 (2–9)	1	4.5	5.0
NF/FIAD*	4	7.3 (6.5–10)	7.3 (4–9)	1	5.0	6.0
UAD	9	7.0 (5–9)	7.0 (5.5–8)	11	8.0 (5–10)	5.5 (2–10)

NFIAD, non-food-induced atopic dermatitis; FIAD, food-induced atopic dermatitis; UAD, unidentified atopic dermatitis. *Dogs with both NFIAD and FIAD.

[14]; namely, that antihistamines should only be used to prevent acute flares and are likely of no benefit in chronic AD.

Moreover, the ICADA suggested that in the absence of convincing clinical trials, veterinarians should limit their prescription to drugs (hydroxyzine, cetirizine) with demonstrable inhibitory effects on intradermal histamine injections in healthy or *Ascaris*-sensitized dogs [1,5]. However, our study clearly indicated that the effects of cetirizine in a clinical trial with dogs with AD differed from those observed under these experimental conditions.

To avoid drug interference from medication administered before inclusion, all drugs were withdrawn prior to the start of the placebo-controlled study. Optimal withdrawal times (OWT), which are defined as those associated with no drug interference, were used [17]. Because the OWT for antihistamines is 7 days, these findings indicate that the effects of antihistamines will disappear in that period of time. Conversely, a positive effect, if any, on pruritus can also be expected in such a period. However, to ensure the potential efficacy of cetirizine, the drug was administered for 14 days in the present study [2]. Nevertheless, no effect of cetirizine on pruritus was observed.

The reported heterogeneity in efficacy of antihistamines has also been attributed to inappropriate doses [16]. The recommended dose of cetirizine applied in clinical practice varies between 0.5 and 1.0 mg/kg administered once daily [2,22]; therefore, a higher (3 mg/kg once daily) dose was used in our study. However, this higher dose of 3 mg/kg did not result in a difference in treatment outcome between placebo- and cetirizine-treated dogs.

Interestingly, this higher cetirizine dosage was tolerated well by the majority of dogs in the trial. Only one dog gave appeared to sleep more than usual, which was likely because of the potential mild sedative effects of cetirizine. These findings agree with those of previous studies [3] indicating that side effects upon cetirizine treatment are rare.

The pruritus VAS used in our study [21] is a validated scale employed to assess the severity of pruritus in dogs that has been shown to be a valuable tool for clinical assessment of patients, as well as for monitoring treatment responses in clinical trials of anti-pruritic drugs. In particular, comparison of the median pruritus scores before and after treatment is preferred to using the number of dogs showing a 50% improvement as a primary outcome measure [21]. Apart from the VAS, there are severity scales to grade skin lesions in clinical trials, such as CADESI-04 [18]. However, these scales are more useful in long term studies [10]. This is because the pruritus will decrease upon initial treatment, which is followed by improvement skin lesions over time, as the latter commonly are the result of scratching.

In summary, our randomized, double blind, placebo-controlled study clearly demonstrated that the H1 histamine receptor antagonist cetirizine has no effect on pruritus in dogs with chronic non-food-induced or food-induced atopic dermatitis. Hence, such medication should not be recommended for the control of pruritus in dogs with long term allergy.

Acknowledgments

Conflict of Interest

There is no conflict of interest.

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