

# THE EFFICACY OF ANTIHISTAMINE FEXOFENADINE VERSUS METHYLPREDNISOLONE IN THE TREATMENT OF ATOPIC DERMATITIS IN DOGS

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**Summary:** The objective of the study was to establish efficacy of antihistamine fexofenadine in atopic dogs. Thirty atopic dogs over the age of 6 months, of different breeds and sex were randomized into two groups with 15 dogs each. The group F received fexofenadine orally; the group M received methylprednisolone for the period of 6 weeks. CADESI and pruritus score were measured three times during the study (at the baseline, after 3 weeks and after 6 weeks of treatment).

Statistically significant discrepancies in CADESI score in comparison with baseline were observed in both groups, namely for 3rd (P=0,007 for group M and P=0,019 for group F) and 6th treatment week (P<0,001 for group M and P<0,001 for group F). Between the groups statistically significant difference in CADESI score for the 6th week of treatment was observed in favour of group F (P=0,012). Statistically significant lowering of strengths of itching score at week 3 (P=0,002) and week 6 (P=0,004) were observed in group M compared to baseline. The difference in strength of itching score in group F was not statistically significant at week 3 of treatment (P=0,215) but was at week 6 of treatment (P=0,002). Between the groups the difference was statistically significant at baseline (P=0,048), although not at week 3 and 6 of treatment. The results of the study are showing comparable improvement of clinical signs for fexofenadine treatment versus methylprednisolone treatment, nevertheless fexofenadine needed longer period of time to reach efficacy endpoint.

**Keywords:** fexofenadine hydrochloride; methylprednisolone; atopic dermatitis; atopy; glucocorticoids; antihistamines

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## Introduction

Atopy is the genetic predisposition of the body to develop immunoglobulin E (IgE) antibodies in response to environmental allergens, which is clinically manifested by a combination of immediate and delayed signs of allergy (1,2,3,4). Symptomatic treatment of atopic dermatitis in dogs often includes glucocorticoids, antihistamines, or a combination of both. While glucocorticoids are highly effective in this indication, their use in long-term treatment causes serious adverse reactions in most patients. Therefore glucocorticoids are main-

ly recommended in acute allergic episodes and for initial treatment of atopy (5,6). The evidence for antihistamine therapy in dogs is still limited but there is a consensus that they offer some benefit, which is worth trying (7). There are some data regarding antihistamines which block H1 receptors could contribute to pruritus control associated with atopic disease in dogs (8,9,10). The realistic success ranges from 5 - 30% for any given antihistamine (11). The sedative effect of many antihistamines may also contribute to the control of pruritus. Some other antihistamines such as tricyclic piperidine antihistamine (azatadin) and hydroxyzine hydrochloride (HCl) may stabilize mast cells and decrease mediator release following antigen challenge in allergic patients. Antiserotonine-, an-

algescic- and antianxiety activity are also expressed by some antihistamines and these may contribute to their effectiveness. In a retrospective study of 55 cases of pruritus in atopic dogs, 30% of the cases responded to antihistamines well enough that the clients were satisfied with the results and the dogs did not require systemic glucocorticoids (12). There are some products that combine antihistamines and glucocorticoids. When prednisone and trimeprazine were given in combination at the same doses 76.7% responded satisfactorily (13). By controlling whichever of the pruritus that is mediated by histamine the patient moves closer to going below its purity threshold.

*Fexofenadine* is a second-generation antihistamine and it is indicated in humans for the relief of symptoms associated with seasonal allergic rhinitis and chronic urticaria. It is a pharmacologically active metabolite of terfenadine, an antihistamine of the first generation. The second-generation antihistamines are more lipophobic than those of the first generation; therefore they do not cross the blood-brain barrier to produce CNS effects and are devoid of anticholinergic activity when used in therapeutic doses (14). In humans it has been shown as highly effective (15,16,17,18,19,20). Fexofenadine has been shown to inhibit the expression of the cell surface adhesion molecule ICAM-1 on human conjunctival epithelial cells (21). It also inhibits eosinophil-induced release of soluble ICAM-1 and induction of inflammatory mediators (e.g. GM-CSF, IL-8) in nasal epithelial cells cultured from biopsies taken from patients with SAR and calcium ionophore-induced release of eosinophil cationic protein from eosinophils (22). In addition, fexofenadine decreases adhesion and chemotaxis of eosinophils to human endothelial cells (23). Consequently, these data suggest fexofenadine has anti-allergic properties in addition to its antihistamine activity in humans.

Fexofenadine does not interact with muscarinic receptors in people and does not provoke drowsiness, urinary retention, dry mouth, and constipation (24), which might offer a potential advantage compared with desloratadine, the recently approved active metabolite of loratadine. Fexofenadine is devoid of adverse cardiac effects, and changes in human electrocardiogram parameters are not significantly different from those observed with placebo (25). It is also well tolerated in people with renal or hepatic impairment, in children and the elderly (26).

Fexofenadine has also been shown to have a favorable effect on nasal congestion. This therapeutic advantage might be related to its significant antiallergic properties (25).

Fexofenadine (as cetirizine and loratadine) may have additional activity at cells involved in the inflammatory response. These actions include possible inhibition of mediator release from mast cells, action on leukotrienes and prostaglandins involved in the late phase allergic response (27,28,29,30).

Cumulatively, these benefits distinguish fexofenadine from the other antihistamines and make it an optimum therapeutic option for treating allergy-mediated respiratory and dermatologic diseases in humans (25).

Any data on the efficacy, safety and recommended doses of fexofenadine hydrochloride in dogs with atopic dermatitis were found in reviewing the literature. Our decision to conduct a study to investigate the efficacy of fexofenadine in the treatment of atopic dogs was therefore made.

## Material and methods

Thirty dogs of different breeds, age and sex with signs of atopic dermatitis and meeting the criteria proposed by Willemse (31) were included in the study. Presentation of the breeds was as follows: 4 german shepherds, 3 chow chows, 3 golden retrievers, 3 mixed breeds, 2 shar-peis, 2 west highland white terriers, 2 labradors, 2 tibetan terriers and one of dalmatian, french bulldog, boxer, cairn terrier, russian terrier, schipperke, basset hound, great dane and cocker spaniel. The age of dogs included ranged from 9 to 125 months (on average 39.5 months). Female gender dominated (18 dogs of 30) and weights ranged from 7.0 kg to 69 kg (on average 27.35 kg).

Other differential diagnoses were excluded before the inclusion into the study. Parasitic diseases were excluded by negative skin scrabs and use of Stronghold spot-on® (Pfizer Ltd., Sandwich, United Kingdom) as a diagnostic therapy trial to exclude scabies. Parasitic diseases were prevented during the study using Frontline spot-on® (Merial, Lyon, France). Prior inclusion into the study individually adjusted elimination diet was fed to the dogs. The dogs have been given elimination diet already 3 months before inclusion into the study and all the time of the study (6 additional weeks).

The study protocol included consent of the dog's owner to participate in the study, data on the animal and the history of the disease and on previous treatments. The use of the following medications was prohibited: glucocorticoids (3 weeks or less before inclusion), antihistamines (14 days or less before inclusion), cyclosporines (1 month or less before inclusion), EFA (14 days or less before inclusion), vitamin E supplements (14 days or less before inclusion), antipruritic substances as SRI (Clamipramin) and SSRI (Fluoxetine) (14 days or less before inclusion), antiseborrheic, keratolytic and antiseptic shampoos (14 days or less before inclusion), immunotherapy (never).

Next conditions were incorporated among the exclusion criteria: the cases with their history, previous therapies and outcomes of the treatments which were not well documented, presence of concurrent illnesses, that could influence the results of the study (like heart disease), serious impairment of kidney or liver function, planned or coincidental pregnancy, FAD symptomatic dogs, concurrent food allergy or intolerance cases not controlled with the diet, presence of the ectoparasites, symptoms of bacterial or fungal concurrent infection.

A random sample was obtained by alternate allocation of dogs to one or the other investigational group. Fifteen dogs were treated for 6 weeks with methylprednisolone (Medrol®, Pharmacia Enterprises S.A.) 0.5 mg/kg/24 hours for the first 5 days, then with 0.5 mg/kg/48 hours (group M), and 15 dogs with fexofenadine (Telfast®, Aventis pharma) 18 mg/kg/24 hours (group F). CADESI-02 (Canine Atopic dermatitis Extent Severity Index) values and pruritus values were taken three times during the study (baseline, after 3 weeks of treatment and after 6 weeks of treatment). Presence and intensity of erythema with lichenification and excoriation of the skin was estimated on altogether 40 different parts of the body. In accordance to photo scale, which was produced prior the study on basis of photographs of clinical cases, every each parameter was scored from 0 to 3 (0 = no changes). The measurements were performed single blindly, thus leaving assessors unaware of previous measurements. Acquired CADESI score was statistically compared between the groups and periods of the treatment.

The pruritus of the skin was estimated on basis of owner observations in each dog. To estimate the pruritus, visual analogue scale was used, for owners

to give their observations by scoring from 0 to 100 (0= no pruritus). The estimate of the owner based on observations regarding intensity, frequency and duration of the pruritus. The owners were instructed to observe licking of the paws and inguinal area, biting of the paws and body, scratching the head and the body as well as rubbing of the head and the body to objects.

The results acquired at the first visit (inclusion day) were compared to the results of the second visit (3 weeks of treatment) and the third visit (6 weeks of the treatment). Results of the second visit were compared to results of the third visit as well. After this, results were compared also between the groups. For the statistical analysis of the obtained data SPSS statistical package version 14 was used. Statistical evaluation of the data between the groups was performed by one-way T test, while statistical evaluation of the data between the visits in each of the groups was performed by ANOVA. Differences were considered significant when  $P < 0.05$ .

The study was approved by the Ministry of Agriculture, Forestry and Food, by its Decision No 4.4.-43/05 issued on 26 October 2005.

## Results

The results of the study are presented in Table 1 and Figures 1-2.

Side effects during the therapy trial:

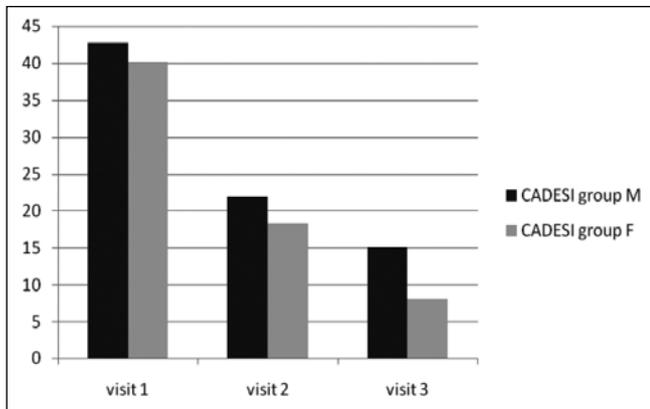
Owners of dogs with numbers 27 and 33 (group M) reported increased drinking of the animals. Three owners of dogs from group M (dogs with numbers 14, 25 and 29) reported on severe fatigue with one of them also with increased eyes discharge. Eyes discharge was reported also by three owners of dogs from group F ( dogs with numbers 11, 16 and 20) at the second visit, one of them also with nasal discharge. Dog number 1 (group F) had for a short while no appetite, although appetite returned when diet flavour changed. Dog from group M with number 15 had transient diarrhoea, with rattle and bacterial inflammation of the abdominal skin occurring at the visit 3. The occurrence of rash was noted also in dog number 13 (group F) at visit 2. By the visit three the rash didn't resolve, on the other hand the dog appeared to be in heat. Due to sporadic and mild nature of difficulties, none of the dogs was excluded from the study.

**Table 1:** CADESI (Canine Atopic dermatitis Extent Severity Index) evaluation at visits 1, 2 and 3 (baseline, after 3 weeks of treatment and after 6 weeks of treatment) for group M (methylprednisolone treated) and for group F (fexofenadine treated)

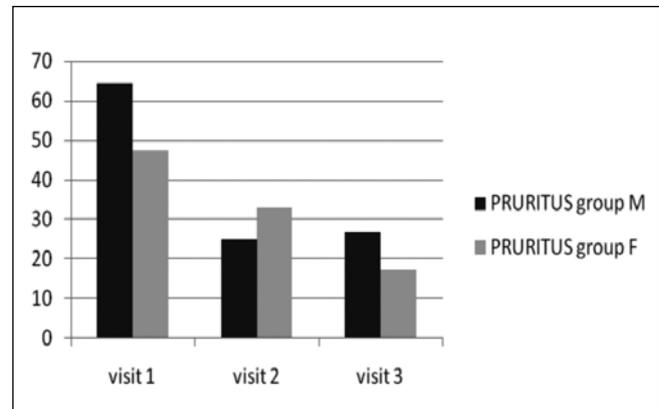
Group M	1.VISIT	2.VISIT	3.VISIT	Group F	1.VISIT	2.VISIT	3.VISIT
3	28	29	25	1	66	42	16
4	13	23	9	2	134	40	13
8	40	29	15	5	19	2	2
10	37	23	11	6	46	14	13
12	62	17	17	7	49	27	18
14	46	18	7	9	24	14	5
15	50	14	17	11	27	10	5
17	11	4	5	13	26	26	22
19	27	12	12	16	43	30	7
23	83	43	32	18	22	9	3
25	60	20	15	20	36	10	6
27	38	11	15	22	34	10	2
29	28	8	8	24	37	5	5
32	45	44	27	26	18	4	2
33	73	44	11	30	20	2	2

Majority of dogs from both study groups experienced lowering of CADESI score parameters from the start to conclusion of the treatment, which was later on statistically evaluated. The dogs with num-

bers 3 in group M and number 13 in group F stepped out, since they haven't experienced lowering of the scores.



**Figure 1:** Mean values of CADESI (Canine Atopic dermatitis Extent Severity Index) at visits 1, 2 and 3 (baseline, after 3 weeks of treatment and after 6 weeks of treatment) for group M (methylprednisolone treated) and for group F (fexofenadine treated)



**Figure 2:** Mean values of pruritus in percent at visits 1, 2 and 3 (baseline, after 3 weeks of treatment and after 6 weeks of treatment) for group M (methylprednisolone treated) and for group F (fexofenadine treated)

## Discussion

Antihistamines are commonly used for treatment of atopic dermatitis in dogs, both as single agents, and as synergistic medications used to re-

duce required dosages of glucocorticoids. While the role of histamine-regulated responses in atopic dermatitis is well-established, antihistamines are not as effective as glucocorticoids in the management of the pruritus in atopic dogs (5). The efficacy of an-

tihistamines is notoriously unpredictable and individualized in a given patient. Part of this variation may be dose-related because antiallergic effects are concentration dependent and some dose ranges are antiallergic whereas others may enhance mediator release (32). We also know that not all the effects of histamine in dogs are antagonized by H1 blockers therefore antihistamines of the second generation, that additionally may block mediator release (33) should be more effective. However the data demonstrate that these drugs are much more effective when given before the allergy symptoms take hold and that they will be most effective if used regularly as directed, starting just before the allergy season which is hard to obtain in treatment of atopic dogs.

In our study Fexofenadine was used that was not used in clinical trials in dogs before. A comparable efficacy of fexofenadine versus methylprednisolone was found, as shown above and discussed below. Two non-responders were observed concerning CADESI score (table 4) but even in these two dogs the pruritus was reduced for more than 50% at the end of the study (data not shown).

Some non-desired effects were observed during the treatment: polydipsia, fatigue, eye discharge, diarrhoea and pyoderma were observed in group M. In group F eye and nasal discharge, loss of appetite and skin rash were reported in few cases. Similar effects (fatigue, diarrhoea) were described in use of fexofenadine in people, but the incidence was similar to placebo (34). According to these data and since observed phenomena in our study were sporadic they can hardly be contributed to the drugs used in short-term therapy. Many of them may also have been symptoms of AD. While the side effects of long-term use of methylprednisolone were already well recognised, fexofenadine long-term use should be additionally investigated.

Developing *fexofenadine* usage in human medicine produced pharmacological studies in dogs. Different ECG parameters regarding possible drug effects were followed and established, that *fexofenadine* perorally in dosage of 30 mg/kg/ body mass twice daily is free of lengthening of QT interval in dogs. Plasma concentrations of *fexofenadine* in dogs were thus reaching 9-time therapeutic plasma concentrations of adult human, who received maximal recommended daily dose of fexofenadine (16). Therefore when formulating the study design we didn't want to exceed the maximal dose that was reported to be safe in dogs. On the other hand our decision about the dose to be used (18 mg/kg b.w.) was based

on the ratio calculated for those antihistamines for which the doses for humans and for dogs were known. The mean doses used in veterinary medicine in dogs are 7.5 times higher than the human recommended dose. The mean human recommended dose of fexofenadine hydrochloride is 180 mg/day. If this dose is adjusted to the average human body mass approximately 75 kg, we get a dose of 2.4 mg/kg b.w. The dose used in the study in dogs was 18 mg/kg b.w. or 7.5 times the human recommended dose. This was the highest acceptable number of tablets administered in a single dose. Optimisation of dosage regimen is left to be determined with further investigation.

In the study CADESI-02 scale was used and was the most up-to-date rating system at the time of the study. CADESI evaluation system is the only system allowing statistical evaluation and monitoring of the effects of the treatment in atopic dogs. A reduction in the mean CADESI scores was observed in both groups of dogs and continued throughout the study period (Figure 1). The difference in the scores at the second visit (3 weeks of treatment) was of statistical significance compared to baseline in both groups ( $P = 0.002$  for group M;  $P = 0.019$  for group F). A statistically significant difference in the mean scores compared to baseline was also found in both groups at the end of the study ( $P < 0.001$  for group M;  $P < 0.001$  for group F). No statistically significant differences between the groups were found at the first visit ( $P = 0.775$ ) and at the second visit ( $P = 0.535$ ), while at the third visit a statistically significant difference ( $P = 0.012$ ) was recorded in favour of group F. It has thus been demonstrated that the clinical picture improved significantly after both investigational therapies. In the last three weeks of the treatment, an even greater improvement was observed in dogs treated with fexofenadine compared to methylprednisolone. Improvement was manifested as reduction or disappearance of skin lesions, i.e. erythema, lichenification and excoriation, as evaluated by the CADESI scoring system. The authors of a similar study (11) set the level of significance for the change of the CADESI score at 50% (CADESI<sub>50</sub>) reduction from baseline. Considering the recommendations of the above authors, we can see that both active substances used in our study reduced the CADESI score by more than 50%, which demonstrates that both medicinal products are sufficiently effective in the treatment of dogs with atopic dermatitis.

The severity of pruritus was markedly reduced compared to baseline in group M at the second visit

(3 weeks of the treatment) and stayed at a similar level until the end of the study (Figure 2). The difference in the severity of pruritus in group M was statistically significant compared to baseline at the second visit ( $P = 0.002$ ) and at the third visit ( $P = 0.004$ ). In group F, the severity of pruritus was gradually decreasing throughout the study period, but the change from baseline at the second visit was of no statistical significance ( $P = 0.215$ ). However, a statistically significant difference was demonstrated at the third visit ( $P = 0.002$ ). This finding demonstrates that both fexofenadine and methylprednisolone therapy resulted in a significant reduction in pruritus in atopic dogs. With methylprednisolone, a significant reduction in pruritus was found as soon as after three weeks, while with fexofenadine a longer period was needed for a similar effect. The between-group comparison by visit revealed a statistically significant difference at the first visit ( $P = 0.048$ ), when the mean severity of pruritus was greater in group M, while no statistically significant differences were found at the second ( $P = 0.47$ ) and third visit ( $P = 0.263$ ). Preliminary study, that was done on 8 dogs remitted encouraging results (35), so the study presented in this article was designed. A comparison of the results of our study with those of a similar study (11), where a reduction in the severity of pruritus by 50% was considered satisfactory, reveals that the mean pruritus severity was reduced in our population of dogs by more than a half (pruritus<sub>50</sub>) over a treatment period of 6 weeks. Therefore both investigational active substances resulted in a satisfactory reduction of the severity of pruritus in dogs with atopic dermatitis.

## Conclusion

Based on the results of this study, we can conclude that both of the active substances, fexofenadine hydrochloride in oral doses of 18 mg/kg b.w. once daily and methylprednisolone in doses of 0.5 mg/kg b.w. administered for 5 days, followed by doses of 0.5 mg/kg b.w. every other day, were effective in reducing the severity of pruritus and the presence of skin lesions (CADESI score) in dogs with atopic dermatitis.

The results of this study suggest that *fexofenadine hydrochloride* could be accepted in the doctrine of treatment of atopic dermatitis in dogs.

However, additional studies will be needed to further substantiate our conclusions and confirm the findings of this study.

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