Managing atopic dermatitis in dogs: are antihistamines as effective as glucocorticoids?

A Knowledge Summary by

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ISSN: 2396-9776
Published: 18 Nov 2020
in: The *Veterinary Evidence* journal Vol 5, Issue 4
DOI: 10.18849/VE.V5I4.335
Reviewed by: Louise Buckley (PhD FHEA RVN) and James Swann (MA VetMB DACVIM DECVIM MRCVS)
Next Review Date: 02 Apr 2022

KNOWLEDGE SUMMARY

PICO question

In dogs with atopic dermatitis, are antihistamines as effective as glucocorticoids at reducing the severity of clinical signs?

Clinical bottom line

Category of research question

Treatment

The number and type of study designs reviewed

Two randomised control trials and one crossover placebo-controlled trial

Strength of evidence

Critical appraisal of the selected papers meeting the inclusion criteria collectively provide weak evidence in terms of their experimental design and implementation

Outcomes reported

The outcomes reported were conflicting. Two studies reported that fexofenadine may be as effective as methylprednisolone at reducing the severity of clinical signs after 6 weeks of treatment however, the study size was small in one and there was limited reporting of the data in the other. The third study, the crossover placebo-controlled trial, tested a variety of antihistamines and prednisone with limited reporting of statistical analysis of the data and found that antihistamines did not provide a sufficient reduction in pruritus unless combined with prednisone

Conclusion

In view of the strength of evidence and the outcomes from the studies, there is insufficient quality of evidence to answer the PICO question and further comparative study is needed

How to apply this evidence in practice

The application of evidence into practice should take into account multiple factors, not limited to: individual clinical expertise, patient's circumstances and owners' values, country, location or clinic where you work, the individual case in front of you, the availability of therapies and resources.

Knowledge Summaries are a resource to help reinforce or inform decision making. They do not override the responsibility or judgement of the practitioner to do what is best for the animal in their care.

Clinical Scenario

You are presented with a 3-year-old, male neutered, Labrador Retriever with a history of non-seasonal pruritus affecting the feet, face, axillae and groin that has recently increased to a moderate level. He has previously been diagnosed with atopic dermatitis and had been treated with topical chlorhexidine shampoo once weekly and oral administration of sarolaner (Simparica, Zoetis UK Ltd) monthly. Clinical examination, coat brushing, trichography and cytology show no evidence of ectoparasites, microbial overgrowth or infection. As pruritus has increased to a moderate level, and given the relatively widespread distribution, you would like to prescribe a systemic medication to help manage pruritus in the short-term. The owner's financial restrictions limit you to either glucocorticoids or antihistamines. Glucocorticoids are known to be effective in managing atopic dermatitis but adverse effects are common even with short-term use e.g. polydipsia, polyuria, polyphagia, panting and more uncommonly lethargy, diarrhoea, vomiting or gastric ulceration. Antihistamines have far fewer adverse effects, although they may cause sedation. However, are antihistamines as effective as glucocorticoids?

The evidence

Three papers were found that answered the PICO question directly; two randomised control trials and one crossover placebo-controlled trial. Plevnik et al. (2009) directly compared the effects of methylprednisolone and fexofenadine to control pruritus and clinical lesions in dogs with atopic dermatitis. Plevnik et al. (2006) performed a small, non-blinded, preliminary trial comparing the safety and efficacy of fexofenadine against methylprednisolone in dogs with atopic dermatitis. Paradis et al. (1991) reported a crossover placebo-controlled trial comparing six medications with placebo. Dogs with atopic dermatitis, flea bite hypersensitivity and an undiagnosed cause of pruritus were used in the study. The treatments given were: clemastine, prednisone, astemizole, doxepin, trimeprazine and trimeprazine combined with prednisone.

Summary of the evidence

Plevnik et al. (2009)	

Population:	Client owned dogs of different breeds, age and sex with a clinical diagnosis of atopic dermatitis that showed signs compatible with the criteria set out by Willemse (1986). Exclusion criteria included:
	• Inadequately documented disease or therapy
	• Other health conditions that may have affected the study outcome (e.g. cardiac, liver or kidney disease)
	• Pregnancy
	• Flea bite hypersensitivity
	• Food allergy if not well controlled or if insufficient investigations were performed to rule this out
	• Ectoparasites, bacterial or fungal infections
	• Been prescribed any of the following:
	  ○ Glucocorticoids within the last three weeks
	  ○ Antihistamines within the last 14 days
	  ○ Ciclosporin within the last 30 days
	  ○ Essential fatty acids within the last 14 days
	  ○ Vitamin E supplements within the last 14 days
	  ○ Serotonin reuptake inhibitors and selective serotonin reuptake inhibitors within the last 14 days
	  ○ Antimicrobial, antiseborrheic and keratolytic shampoos within the last 14 days
	  ○ Immunotherapy

Sample size:	30 dogs divided equally between groups (15 in each)
Intervention details:	• Skin scrapings and a treatment trial with Stronghold Spot-On (Zoetis UK Ltd.) were used to rule out ectoparasites, including sarcoptic mange, in all dogs prior to study inclusion. • All dogs were fed an individualised elimination diet for 3 months prior to and for the duration of the study. • Dogs were randomly allocated to two treatment groups by alternate allocation. • Group M (n = 15) were given methylprednisolone orally at 0.5 mg/kg/24hrs for 5 days then 0.5 mg/kg/48hrs. • Group F (n =15) were given fexofenadine orally at 18 mg/kg/24hrs. Patients were evaluated at days 0, 21 and 42. • All dogs were treated with fipronil (Frontline Spot-On, Boehringer-Ingelheim) topically during the trial period.
Study design:	Randomised control trial
Outcome studied:	Objective measurements: 1. CADESI-02 (Canine atopic dermatitis extent severity index) scores; 2. PVAS (pruritus visual analogue scale) scores. CADESI-02 scores were achieved using a scale of photographs of clinical signs to estimate the presence and intensity of erythema, lichenification and excoriation of 40 body parts. These lesions were scored from 0–3 (0 = no skin changes). The assessors were blinded to the patient's previous scores. PVAS scores were provided by owner assessment and ranged from 0 (0 = no pruritus) to 100. Statistical evaluation of the data between groups was performed using the one-way T test. Evaluation of the data between the visits in each group was performed using analysis of variance (ANOVA). Significance was set at $p<0.05$.
Main findings: (relevant to PICO question):	• There is very limited reporting of the data. Individual CADESI-02 scores are provided for each dog at all three time points but PVAS scores are not. Means of both scores were used for analysis but are only reported in a bar chart and the numbers themselves are not provided. Mean CADESI-02 scores can be calculated from the data in table 1 but there is insufficient reporting of the data to calculate mean PVAS scores. • Group M: mean CADESI-02 score was significantly lower on day 21 (22.60, $p = 0.002$) and day 42 (15.07, $p<0.001$) compared to day 0 (42.73). Mean PVAS score was significantly lower at day 21 ($p = 0.002$) and day 42 ($p = 0.004$) compared to day 0. • Group F: mean CADESI-02 score was significantly lower on day 21 (16.33, $p = 0.019$) and day 42 (8.07, $p<0.001$) compared to day 0 (40.07). Mean PVAS score at day 21 was not significantly different from day 0 ($p = 0.215$) but there was a significant difference by day 42 ($p = 0.002$). • Group F had a significantly lower mean CADESI-02 score at day 42 compared to Group M (8.07 and 15.07, $p = 0.012$).

	Group M had a higher mean PVAS score compared to Group F at day 0 (p=0.048) but not at day 21 or 42. • Group M dogs showed at least a 50% decrease in CADESI-02 score compared to day 0 in 8/15 dogs (53.3%, 95% CI 30.1-75.2%) and 11/15 dogs (73.3%, 95% CI 48.1–89.1%) at day 21 and 42 respectively. Group F dogs showed at least a 50% decrease in CADESI-02 score compared to day 0 in 10/15 dogs (66.7%, 95% CI 41.7–84.4%) and 13/15 dogs (86.7%, 95% CI 62.1–96.3%) at day 21 and 42 respectively. • Both medications showed significant improvements in clinical assessment and pruritus at the end of the trial. The authors comment that fexofenadine may have a greater effect than methylprednisolone with longer-term use but was less effective at controlling pruritus during the first 3 weeks of treatment.
Limitations:	• The dose of fexofenadine used was calculated based on previous safety studies and comparative doses of other antihistamines. A study assessing the effective dose range prior to comparison with methylprednisolone would have been useful. • Group M had a significantly higher PVAS score on day 0 compared to Group F which may have introduced bias to the results. As the data is not provided it cannot be determined if this is due to one outlier or an overall group difference. • The authors did not discuss if endocrine disease was investigated or excluded with blood and urine testing prior to enrolment. • A 'rash' was noted in one dog in Group F on day 21 that had not resolved by day 42. This dog was in season during that time frame and the authors suggest this may be associated with the lack of resolution of the rash. To help minimise potential variation associated with changes in hormone levels, bitches due in seasons during the trial period should have been excluded. • There was very little presentation of the data obtained in the results section in particular for PVAS scores. Statistical analysis was also not reported in the results and first appears in the discussion. A one sample T-test was not appropriate to compare the means of two groups. It is not clear if repeated measures or one-way ANOVA was used for the evaluation of data between the visits. • Confidence intervals were not provided and when calculated for at least a 50% decrease in CADESI-02 scores from day 0 to 21 or 42 are wide. There is no visual representation of data dispersion in the bar charts either. • There is no information about the power of the study and why a sample size of 30 dogs was chosen. • CADESI-02 and PVAS are both validated scales; CADESI-02 has now been through two amendments to become CADESI-04 (Olivry et al., 2002; Olivry et al., 2014; and Rybníček et al., 2009). However, their measurements are based on human

	perception adding a degree of subjectivity to them • The lead author is employed by the manufacturer of fexofenadine which may have introduced bias.

Plevnik et al. (2006)	
Population:	Client owned dogs over 6 months of age, of varying breeds and both sexes, with a clinical diagnosis of atopic dermatitis showing signs compatible with at least three major and two minor criteria as described by Willemse (1986). Patients were excluded for the reasons below: • Inadequately documented disease or therapy • Other health conditions (e.g. cardiac, liver or kidney disease) • Pregnancy • Flea bite hypersensitivity • Food allergy if not well controlled or if insufficient investigations performed to rule this out • Ectoparasites, bacterial or fungal infections • Were prescribed any of the following: o Glucocorticoids within the last 3 weeks o Antihistamines within the last 14 days o Ciclosporin within the last 30 days o Vitamin E supplements within the last 14 days o Serotonin reuptake inhibitors and selective serotonin reuptake inhibitors within the last 14 days o Antimicrobial, antiseborrheic and keratolytic shampoos within the last 14 days o Immunotherapies
Sample size:	Eight dogs randomly allocated to two groups
Intervention details:	• Four dogs were allocated to each treatment group; the method of randomisation is not reported. • Group F (n = 4) were treated with 18 mg/kg/24hrs fexofenadine orally and • Group M (n = 4) with 0.5 mg/kg/24hrs methylprednisolone orally for 5 days, then every other day. • Treatment was continued for 6 weeks and assessments made at days 0, 21 and 42.
Study design:	Randomised control trial (non-blinded)
Outcome studied:	Objective measurements for each group were: • Aspartate aminotransferase (AST); Alanine aminotransferase (ALT); Alkaline phosphatase (ALKP) (however as these measurements are not relevant to the PICO the results will not be commented in this summary) • Urea • Creatinine • CADESI (lesion) score performed by clinician • Pruritus score (PVAS) performed by owners (0–100, 0 = no pruritus) Statistical evaluation of the data was performed using the one-way Student's T-test and results were considered significant if p<0.0.5.

	Results were compared between each visit at days 0, 21 and 42 and between groups.
Main findings: (relevant to PICO question):	• In Group F CADESI was significantly lower at day 42 (mean 4.25) compared to day 0 (mean 30.00, p = 0.011) but not at day 21 (mean 14.00, p = 0.102). • In Group M CADESI was not significantly different from day 0 (mean 31.25) at day 21 (mean 20.00, p = 0.470) and day 42 (mean 13.00, p = 0.171). • In Group M PVAS score was significantly lower at day 21 (mean 3.75, p = 0.004) and day 42 (mean 17.50 p = 0.022) compared to day 0 (mean 56.25). • In Group F PVAS score was not significantly different from day 0 (50.00) at day 21 (33.75, p = 0.668) or day 42 (23.75, p = 0.374). • There was no significant difference between day 0 and days 21 or 42 for AST, ALT, ALKP, urea or creatinine in either group. • CADESI scores were not significantly different between Group F and Group M at day 0 (p = 0.898), day 21 (p = 0.500) and day 42 (p = 0.111). • PVAS scores were not significantly different between Group F and Group M at day 0 (p = 0.625), day 21 (p = 0.078) and day 42 (p = 0.736). Both medications reduced mean CADESI and PVAS scores by at least 50% at day 42 compared to day 0. Individual CADESI and PVAS scores or measures of variation are not reported.
Limitations:	• Fexofenadine dose was calculated based on other antihistamine doses and an acceptable number of tablets to give orally rather than efficacy studies. • The method of randomisation is not reported. • There was a difference in some baseline biochemistry levels. • The method of randomisation was not explained. • Whilst CADESI and pruritus scores decreased by at least 50% during treatment only methylprednisolone produced a significant reduction in pruritus and fexofenadine a significant reduction in lesion score although this may have been affected by the small group sizes. • As only mean CADESI and PVAS scores are reported, the level of variance around the mean should have been included. The Student's T-test was not appropriate to compare repeated measurements. • The power of the study is not calculated and the sample size of only four dogs per group is likely too small to demonstrate a significant difference. • CADESI and PVAS are both validated scales; CADESI has now been through three amendments to become CADESI-04 (Olivry et al., 2014; and Rybníček et al., 2009). However, their measurements are based on human perception adding a degree of subjectivity to them. • The lead author is employed by the manufacturer of fexofenadine which may have introduced bias.

Paradis et al. (1991)	
Population:	Dogs of variable age, breed and sex that were presented to the University of Montreal with a history of pruritic skin disease ranging from 6 months to 5 and a half years in duration. Non-seasonal atopy was diagnosed using history, clinical signs and compatible reactions on intradermal skin testing. A 3 week diet trial with lamb or fish and rice was used to determine if cutaneous adverse food reaction was present. Flea bite hypersensitivity was diagnosed using history, clinical signs and compatible reactions on intradermal skin testing. Idiopathic pruritus was defined as non-seasonal and not responding to the 3 week elimination diet; these dogs did not receive intradermal testing. None of the dogs had pyoderma at enrolment.
Sample size:	30 dogs: • 21 with non-seasonal atopy • two with non-seasonal atopy and cutaneous adverse food reaction • two with non-seasonal atopy and flea bite hypersensitivity • one with flea bite hypersensitivity • four with non-seasonal idiopathic pruritus
Intervention details:	Each dog acted as its own control. Dogs were treated with each drug individually for 1 week followed by a 2 day wash-out period taking the trial length to 9 weeks in total. The drugs used were (dosages for small (<10kg), medium (10–25kg) and large (>25kg) dogs): • Astemizole (2.5 mg, 5 mg and 10 mg once daily) • Clemastine (0.5 mg, 1 mg and 1.5 mg twice daily) • Doxepin (10 mg, 20 mg and 30 mg thrice daily) • Trimeprazine (5 mg, 10 mg and 15 mg twice daily) • Trimeprazine with prednisone (5 mg and 2 mg, 10 mg and 4 mg and 15 mg and 3 mg respectively, twice daily) • Prednisone (2 mg, 4 mg and 6 mg twice daily) • Placebo (100 mg lactose tablet once daily for all dogs) The trial was double-blinded with neither the owner nor veterinary surgeon were aware of which treatment was being given at any time. Owners were given a data sheet to record daily drug administration and observations. Results were evaluated at the end of trial and discussed over the phone or at the hospital. At the end of the 9 week trial, if one or more of the drugs was deemed effective a further 2 week course of each was given to assess if efficacy was sustained. Where prednisone was effective, including in combination with trimeprazine, the minimal effective prednisone dose was established. Doses of each drug were divided into small dog (<10 kg), medium (10–25 kg) or large (>25 kg) and not calculated on a mg/kg basis. 26/30 dogs were diagnosed with atopic dermatitis; 15/26 atopic dogs started immunotherapy at the end of the study and 4/26 dogs 3 weeks before the end of the study and 7/26 atopic dogs did not start immunotherapy during the study period.
Study design:	Double-blinded crossover placebo-controlled trial

Outcome studied:	• Subjective measurements: improvement in pruritus was recorded by owners as:
	  ○ None-to-worse
	  ○ Poor
	  ○ Good
	  ○ Excellent
	• A satisfactory response was defined as good or excellent with sustained efficacy and unsatisfactory as poor or none-to-worse sustained efficacy.
	• Statistical analysis of the data was limited to correlation between improvement or adverse effects with age, breed, sex, weight, clinical diagnosis and duration of clinical signs. The statistical software and methods used are not defined. Confidence intervals are not provided but can be calculated from the data.
	• Adverse effects for each medication were recorded.

Main findings: (relevant to PICO question):	• Prednisone was the most effective drug with a satisfactory response in 17/30 dogs (56.7%, 95% CI 39.2–72.6%) but showed a greater satisfactory response when used in combination with trimeprazine in 23/30 dogs (76.7%, 95% CI 59.1–88.2%). • Clemastine was the most effective antihistamine with a satisfactory response in 9/30 dogs (30%, 95% CI 16.7–47.9%). • All other medications showed very low levels of satisfactory responses; 1/30 dogs (3.3%, 95% CI 0.6–16.7%) for astemizole and trimeprazine, 0/30 dogs (0%, 95% CI 0–11.4%) for doxepin and placebo. • All of the above 95% confidence intervals were calculated by the author of this knowledge summary and were not reported in the original paper. • No correlation was found between response or adverse effects and age, breed, sex, weight, diagnosis or duration of clinical signs. Adverse effects occurred most commonly with doxepin (4/30 dogs, 13.3%) and included vomiting (2/4 dogs), trembling and panting (2/4 dogs) and lethargy (1/4 dogs). Doxepin was withdrawn in 2/4 dogs due to these adverse effects.
Limitations:	• A more objective measurement of improvement, such as a pruritus visual analogue scale score or veterinary assessment with CADESI scoring, could have added to the study. • Confidence intervals are not reported and when calculated are wide. • It is unclear in what order the medications were given; it is not stated if it is the same order as the table provided or randomised and therefore it is difficult to know if the sequence of medications may have had an influence on results. • Immunotherapy should not have been started during the study period as it may have had an effect on the owner's

	perception of pruritus. • It is not clear why a 7 day treatment period and 2 day wash-out period were chosen. • The doses of antihistamine used are based partly on manufacturer guidelines, but some are based on empirical clinical consensus and a dose determination trial may have been more useful. • Including dogs without a diagnosis for the cause of their pruritus may have influenced the response to treatment. • A 3 week elimination diet trial was not sufficiently long enough to investigate cutaneous adverse food reaction. An elimination diet should be fed exclusively for 6 to 8 weeks (Olivry et al., 2015). • There is no information on why a sample size of 30 dogs was chosen nor the power of the study.

Appraisal, application and reflection

There was relatively little evidence available comparing the efficacy of antihistamines against glucocorticoids in dogs with atopic dermatitis. Paradis et al. (1991) reported the greatest owner satisfaction with oral prednisone, used either alone or in combination with trimeprazine, for the treatment of pruritus in comparison to any of the four antihistamines used as a sole therapy. However, the lack of objective measurements and minimal statistical analysis limits the value of this study. Further subjective bias is added as the outcome was dependent on owner assessment of pruritus and had veterinary assessment of clinical response been performed, this would have strengthened the data. The inclusion of dogs without a confirmed diagnosis will have added another limitation to the data. The choice of a 2 day wash-out period is not explained and is short given that the duration of effect of prednisone is 24–36 hours (Miller et al., 2013); as the sequence of drug administration is not specified this could have influenced the results.

Plevnik et al. (2009) found that methylprednisolone was more effective at reducing pruritus in the short-term than fexofenadine however, at 6 weeks into treatment fexofenadine showed a greater reduction in mean CADESI-02 score than methylprednisolone. The small, non-blinded, preliminary trial carried out by Plevnik et al. (2006) demonstrated a similar ability of fexofenadine to reduce CADESI scores at 6 weeks of treatment. The authors state that both medications are efficacious as they reduced mean CADESI and mean PVAS scores by at least 50% and are comparable as there was no significant difference between the two groups. However, the results of this study may have been influenced by the small number of dogs used and results should be interpreted with caution.

The evidence above is conflicting as whilst two of the studies (Plevnik et al., 2009; and Plevnik et al., 2006) demonstrate some effect of antihistamines on pruritus and CADESI score, Paradis et al. (1991) reported a lack of owner assessed response in pruritus. The International Task Force on Canine Atopic Dermatitis treatment guidelines (Olivry et al., 2010) advise that type-1 histamine receptor antagonists or inverse agonists are unlikely to be beneficial in both acute and chronic atopic dermatitis based on the evidence available. During acute flares antihistamines do not have enough time to block the histamine receptors before histamine is released. Antihistamine treatment is also unlikely to be beneficial in chronic cases of atopic dermatitis. This may be due to a lack of relevance of type-1 histamine receptors in canine atopic dermatitis or inappropriate dosing. There is little evidence to determine the efficacy of antihistamines in mild cases of atopic dermatitis or to prevent future flares however, if given daily its use as a preventative may be beneficial. The guidelines note that only hydroxyzine and cetirizine have proven inhibition of histamine when given by intradermal injection in dogs and recommend either of these if antihistamines are to be used (Bizikova et al., 2008; Olivry et al., 2010; and Temizel et al., 2011).

The International Committee on Allergic Diseases of Animals updated their guidelines on the treatment of canine atopic dermatitis in 2015 (Olivry et al., 2015) and reported that their review of the literature found evidence of a limited quality and consistency demonstrating a small benefit of antihistamines in some dogs consisting primarily of a retrospective survey and a randomised placebo-controlled trial. Antihistamines may be best suited to mild cases or ideally used as a preventative allowing the drug to block the histamine receptors before histamine is released. They also recommend using antihistamines with proven efficacy or bioavailability. It is worth remembering that atopic dermatitis can be variable in its presentation. Some patients may show unvarying severity of lesions all year round however, others may have a seasonal presence or exacerbation of signs. This can make interpreting treatment responses more complicated.

Two of the studies outlined above compared the same antihistamine however, they were performed at the same institute and the lead author on both papers was employed by the manufacturer of fexofenadine introducing potential for bias (Plevnik et al., 2006; and Plevnik et al., 2009). Studies comparing commonly used antihistamines to glucocorticoids and both their short- and long-term effects would greatly improve the evidence base particularly as atopic dermatitis is a chronic condition that often requires long-term medical therapy.

In summary, there is not enough evidence available to answer the PICO question and further randomised controlled trials are warranted to demonstrate if there is comparable efficacy of antihistamines to glucocorticoids.

Methodology Section

Search Strategy	
Databases searched and dates covered:	CAB Abstracts 1973-week 14 2020 on CAB Direct interface PubMed 1900-week 14 2020 on NCBI interface Web of Science 1900-week 14 2020
Search terms:	The search terms below were used on all three databases: (prednisolone OR prednisone OR glucocorticoid* OR steroid* OR cortico-steroid* OR corticosteroid* OR corticoid* OR glucocorticoids OR steroids) AND (antihistamine* OR anti-histamine* OR antihistaminics) AND (atopy OR atopic OR allerg* OR atopic dermatitis) AND (dog OR dogs OR canine OR bitch OR bitches OR canis)
Dates searches performed:	02 April 2020

Exclusion / Inclusion Criteria	
Exclusion:	Review articles, articles not available in English, book chapters and conference proceedings, non-peer-reviewed journals and articles that did not compare antihistamines to glucocorticoids in atopic dogs therefore were not relevant to the PICO question.
Inclusion:	Peer-reviewed, original control studies comparing antihistamines with glucocorticoids in dogs with allergic skin disease.

Search Outcome						
Database	**Number of results**	**Excluded – Not available in English**	**Excluded – Book, conference proceeding or non-peer-reviewed**	**Excluded – Not relevant to PICO question**	**Excluded – Review articles**	**Total relevant papers**
CAB Abstracts	84	19	31	19	14	1
PubMed	45	7	0	29	9	0
Web of Science	39	5	0	24	7	3
Total relevant papers when duplicates removed						**3**

CONFLICT OF INTEREST

The author declares no conflicts of interest.

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