DOI: 10.1111/j.1365-3164.2009.00756.x

Efficacy of a 0.0584% hydrocortisone aceponate spray in the management of canine atopic dermatitis: a randomised, double blind, placebo-controlled trial

Tim Nuttall*, Ralf Mueller†, Emmanuel Bensignor‡, Maite Verde§, Chiara Noli¶, Vanessa Schmidt* and Christophe Rème**

*Small Animal Teaching Hospital, The University of Liverpool, Leahurst, UK
†Faculty of Veterinary Medicine, Ludwig-Maximilian-University, Munich, Germany
‡Clinique Vétérinaire de la Boulais, Cesson Sevigné, France
§Department of Veterinary Dermatology, University of Saragosa, Saragosa, Spain
¶ANUBI Veterinary Hospital, Moncalieri, Italy
**Medical Department, Virbac SA, Carros, France
Correspondence: Dr Tim Nuttall, The University of Liverpool Small Animal Teaching Hospital, Leahurst Campus, Chester High Road, Neston, Cheshire, CH64 7TE. E-mail: timn@liv.ac.uk

Sources of Funding
The study was funded by Virbac SA.
Conflict of interest
C.A. Reme is an employee of Virbac SA. T.J. Nuttall, R. Mueller, E. Bensignor, M. Verde and C. Noli are in receipt of funding from Virbac SA for unrelated studies and/or have acted as consultants for this and other studies.

Abstract

This study evaluated a 0.0584% hydrocortisone aceponate (HCA) spray (Cortavance®; Virbac SA, Carros, France) in canine atopic dermatitis (AD). Initially, dogs with a canine AD extent and severity index (CADESI-03) ≥ 50 were randomly allocated to receive HCA (n = 15) or placebo (n = 13) (two sprays from 10 cm away to treat an area of 100 cm^2) once daily for 28 days. Twenty-one of the dogs then received HCA spray once daily, reducing to every other day or twice weekly over 42 days if improvement was maintained. CADESI, pruritus (14 cm visual-analogue-scale) and owner satisfaction (5-point scale) were recorded every 14 days. Haematology, biochemistry and adrenocorticotrophic hormone stimulation were performed at baseline, d28 and d70 (HCA n = 9; placebo n = 7). Intention-to-treat data were analysed. HCA spray significantly decreased CADESI (–61.4% versus –13.4%, P = 0.0069) and pruritus (–38.8% versus +57.6%, P = 0.0015) at d28 compared to placebo. Scores were significantly decreased at d14 (CADESI –50.5%, P < 0.0021) and d28 (CADESI P < 0.0001; pruritus P = 0.018) compared to baseline following HCA but not placebo. At d28 11 of 15 and 7 of 15 HCA dogs had ≥ 50% reductions in CADESI and pruritus compared to 3 of 13 (P = 0.02) and 1 of 13 (P = 0.04) placebo dogs. Owner satisfaction scores were significantly higher in the HCA group (d28 P = 0.0001). Daily 3 of the 21 dogs required daily maintenance therapy, 7 every other day, 6 twice weekly and 5 dogs required additional therapy. Coat length did not influence the results. No adverse effects or changes to blood parameters were noted. HCA spray proved safe and effective up to 70 days. It is not, however, licensed for long-term treatment.

Accepted 14 January 2009

Introduction

Canine atopic dermatitis (AD) is a common, chronic, inflammatory dermatosis.[1] It is defined as a genetically predisposed inflammatory and pruritic allergic skin disease with characteristic clinical features, and is most commonly associated with IgE antibodies to environmental allergens.[2] It has become clear that canine AD is a complex, multifactorial disease involving interactions between skin structure, the immune system and environmental influences. The complex pathology makes AD a challenging disease to manage. Treatment options include managing flare factors, bathing and skin care, allergen avoidance, allergen-specific immunotherapy (ASIT) and essential fatty acids, but many atopic dogs require long-term anti-inflammatory medication.[3]

Glucocorticoids are inexpensive, easy to administer and highly effective, but systemic treatment frequently results in serious acute and chronic adverse effects.[4] Topical application is an attractive option as this delivers the drug to the site of inflammation, avoiding systemic exposure. Topical preparations containing hydrocortisone, betamethasone, triamcinolone and prednisolone are effective in a variety of inflammatory dermatoses including canine AD.[4–6] Long-term treatment has nevertheless been associated with cutaneous atrophy, ulceration, telangectasia, alopecia, comedones, calcinosis cutis and altered hypothalamic-pituitary-adrenal axis function.[4,7–9]

Nonhalogenated, di-ester topical glucocorticoids avoid many of these problems by virtue of their metabolism into largely inactive moieties within the skin.[10,11] The absence of fluorine or chlorine at C6, C9 or C21 is associated with better local and systemic tolerance compared to conventional topical glucocorticoids.[10,11] Acetate esterification at C21 increases stability, whereas propionate esterification at C17 enhances affinity for the corticosteroid receptor and anti-inflammatory activity.[10,11] Double esterification greatly enhances penetration of the stratum corneum, but also ensures specific metabolism in the deeper dermis. This minimizes effects on hair follicles, dermal fibroblasts and

Table 1. Inclusion and exclusion criteria

Inclusion criteria
1. At least 18 months of age
2. History of perennial pruritus
3. Clinical diagnosis of atopic dermatitis
4. No response to a minimum 6-week novel (home cooked or commercial) or hydrolysed exclusion diet. Dogs should be stabilised on their usual diet for at least 2 weeks prior to the trial, which should be maintained during the study
5. No response to a veterinary approved flea control regimen for at least 8 weeks and monthly flea control maintained throughout the trial
6. Sarcoptic mange excluded by trial therapy and/or negative serology
7. CADESI-03 ≥ 50
8. Allergen-specific immunotherapy (ASIT) permitted if used for > 12 months, the dose remains unchanged for 6 months, the clinical signs are stable and the regimen is maintained during the trial
9. Essential fatty acids permitted if in use for > 8 weeks, the clinical signs are stable and the dosing regimen maintained during the trial
10. Owners' written informed consent has been obtained
Exclusion criteria
1. Clinical evidence of ectoparasite infestation
2. Clinical evidence of bacterial or fungal infections
3. Antimicrobial therapy or prostaglandins within 7 days
4. Antihistamines within 14 days
5. Oral or topical glucocorticoids or ciclosporin within 28 days
6. Parenteral depot glucocorticoids within 56 days
7. Initiated or discontinued essential fatty acids within 56 days
8. ASIT discontinued within six months or initiated within 12 months
9. Pregnancy or breeding activity
10. Concurrent condition that may deteriorate during the study

blood vessels, decreasing the likelihood of local cutaneous and systemic adverse effects.[10,11]

A number of these products are widely used in human dermatology with much improved benefit–risk ratios compared to traditional topical glucocorticoids. Methylprednisolone aceponate (Advantan®; Intendis GmbH, Berlin, Germany) is a highly effective treatment for AD and other forms of eczema with minimal local and systemic adverse effects.[12,13] It is now regarded as a first-line product with an excellent therapeutic index and benefit–risk ratio in medical dermatology.[12,13]

An almost identical topical glucocorticoid, hydrocortisone aceponate (HCA; Cortavance®, Virbac SA, Carros, France), has been licensed in a 0.0584% spray formulation for the short-term treatment of pyotraumatic dermatitis, flea allergic dermatitis and other inflammatory dermatoses in dogs. The purpose of this trial was to assess its efficacy and safety profile in the treatment of canine AD.

Materials and methods

Study subjects

The study was performed in accordance with ethical guidelines laid down by the University of Liverpool, the University of Saragosa, Ludwig-Maximilan-University and Virbac SA. Dogs with a clinical diagnosis of AD according to accepted criteria[14] were recruited from five European dermatology referral centres. It was estimated that with a mean baseline CADESI-03[15] score of 100, a mean 50% reduction in the treatment group and 10% in the placebo group with an SD of ±30%, 15 dogs in each group would detect a statistically significant difference in response to treatment with > 95% power.

Trial protocol

In part one of the trial, 29 dogs with AD that fulfilled the entry criteria (Table 1) were randomly allocated to receive either 0.0584% HCA or placebo spray. Dogs were sequentially allocated to treatment groups A, B, C or D according to a computer-generated random sequence established before the trial. Two groups were active HCA spray and two were the placebo. Four treatment identifiers were used to minimize detection bias that could arise from perceived efficacy or lack of efficacy with only two treatment identifiers. The packaging and nature of the active treatment and placebo were identical. Owners were instructed to apply the spray once daily to affected skin from 10 cm away at a dose rate of two sprays per 100 cm^2 of affected skin. Affected skin was treated as required with no restriction on the body area that could be treated or the number of sprays per animal. All sizes of dog, type of lesions and coat lengths were treated in the same way. Clinical assessments (Table 2) were performed at days 0, 14 and 28.

In part two of the trial all dogs received the 0.0584% HCA spray. There was no wash-out period between parts one and two of the trial. Treatment was initially administered once daily as described. Clinical assessments were performed at days 28, 42, 56 and 70. If the CADESI-03 was ≤ 50 at day 42 (i.e. after 14 or 42 days of daily HCA for dogs on placebo or HCA in part one, respectively) the owners were instructed to administer treatment every other day; if not, once-daily treatment was maintained. At day 56 (i.e. after 28 or 56 days of HCA) treatment was adjusted as follows: CADESI-03 ≤ 25 – administered twice weekly; CADESI-03 26–50 – administered every other day; CADESI-03 > 50 – administered once daily. Additional therapy was given to dogs on daily therapy with a CADESI-03 > 50 at the investigators' discretion.

Outcome measures

The outcome measures were the CADESI-03, pruritus and owner global evaluation (Table 3) scores. The CADESI-03 is a validated assessment of clinical lesions (erythema, excoriation, lichenification and self-induced alopecia) at 62 anatomical sites from 0 (normal) to 5 (most severe) yielding a score of 0–1240.[15] Pruritus was assessed using a horizontal 14 cm visual analogue scale (VAS) marked 'not itchy' at the left edge and 'very itchy all the time' at the right edge. Owners were asked to mark the scale with a short vertical line according to their perception of their dog's pruritus over the preceding 24 h. The pruritus score was the distance in cm from the left edge of the scale to their mark.

Compliance measures

The owners were instructed to document the number of sprays administered each day, concomitant treatments and other events in a diary. The spray bottles were weighed when dispensed and at each

Table 2. Clinical assessments

Pre-inclusion (day 0 and/or earlier)		Signalment
		Medical history
		Recent treatments and concomitant medications
		Haematology and biochemistry
		ACTH stimulation test
Part 1	Day 0	CADESI-03
		VAS pruritus score
	Day 14	CADESI-03
		VAS pruritus score
		Global assessment by owner
	Day 28	CADESI-03
		VAS Pruritus score
		Global assessment by owner
		Haematology and biochemistry
		ACTH stimulation test
Part 2	Day 28	Same visit as D28 above
	Day 42	CADESI-03
		VAS Pruritus score
		Global assessment by owner
	Day 56	CADESI-03
		VAS Pruritus score
		Global assessment by owner
	Day 70	CADESI-03
		VAS Pruritus score
		Global assessment by owner
		Haematology and biochemistry
		ACTH stimulation test

CADESI – canine atopic dermatitis extent and severity index.
VAS – visual analogue scale.

revisit to determine the amount of medication used and whether this tallied with the diary.

Clinical assessments

Investigators performed a thorough clinical examination at each visit, recording and investigating any adverse events as appropriate. At days 0, 28 and 70 samples for haematology and biochemistry were taken and an ACTH stimulation test performed. Briefly, serum was collected for cortisol assay immediately before and 1 h after intravenous administration of 0.25 mg synthetic ACTH (Synacthen®; Alliance Pharmaceuticals, Chippenham, UK).

Data analysis

Dogs were withdrawn if they required treatment with a prohibited medication, experienced unacceptable discomfort or for poor compliance. Owners were free to withdraw their animals at any point. End of dosing assessments were recorded for intention-to-treat (ITT) analyses using the last treatment value carried forward.

Data were tested for normal distribution before analysis (Kolmogorov-Smirnov tests; Instat®, Graphpad Inc., San Diego, CA, USA). Unpaired *t*-tests, Mann-Whitney *U*-tests and Fisher's exact tests (Instat®) were used to compare demographic data between the two groups. A general linear model repeated measures two-way ANOVA with Tukey's post-tests (Minitab® 15; Minitab Ltd, Coventry, UK) was used to compare the CADESI-03 and pruritus scores between the HCA and placebo groups at days 0, 14 and 28, and CADESI-03 and pruritus scores at days 14 and 28 to baseline within each group. Repeated-measure ANOVAs were also used to compare the scores at each time point for dogs with short and medium/long coats in both treatment groups. Fisher's exact tests (Instat®) were used to compare the proportion of dogs that achieved ≥ 50% reductions in CADESI-03 and pruritus scores in each group. Repeated-measure two-way ANOVA was used to compare the owners' global evaluation scores between the two groups at days 14 and 28. For part two of the trial, chi-square tests (Graphpad Inc.) were used to compare the proportions of dogs that received HCA or placebo in part one that could be subsequently maintained on twice weekly, every other day and daily HCA treatment or daily HCA plus additional therapy. Significance was set at $P < 0.05$.

Results

Demographic data

Sixteen dogs from 14 breeds and crosses were enrolled in the HCA group, and 13 dogs from 11 breeds and crosses in the placebo group. The range of breeds did not appear to differ between the groups, but the low numbers of each breed prevented statistical analysis. Coat length was subjectively reported according to type and breed. Coat length was evenly distributed between the treatment groups (chi square test $P = 0.96$): short coat (e.g. boxer, Jack Russell terrier and English bulldog) HCA $n = 7$ and placebo $n = 5$; medium coat (e.g. golden retriever, cocker spaniel and poodle) HCA $n = 8$ and placebo $n = 7$; and long coat (chow and Yorkshire terrier) HCA $n = 1$ and placebo $n = 1$. There were no significant differences in age (HCA – mean 4.7 years, range 1.5–10; placebo – mean 3.7 years, range 1–8 [unpaired *t*-test $P = 0.32$]), sex (HCA – 9 female, 7 male; 7 female, 6 male [Fisher's exact test $P = 0.90$]) or weight (HCA: median 25.6 kg, range 2.1–83; placebo: median 20.1 kg, range 2.7–35 [Mann-Whitney *U*-test $P = 0.50$]). Concomitant treatments included essential fatty acids (HCA $n = 3$; placebo $n = 2$), meloxicam (HCA $n = 1$), ear cleaner (HCA $n = 2$), shampoo (HCA $n = 1$; placebo $n = 2$), ASIT (HCA $n = 2$; placebo $n = 1$), ivermectin (HCA $n = 1$) and levothyroxine (placebo $n = 1$).

Intention-to-treat analyses

Five dogs were prematurely withdrawn: one dog in the HCA group that received prohibited medication after 3 days following a possible adverse reaction (see succeeding discussion), and four dogs on placebo at day 14 as a result of lack of efficacy. There were no on-treatment data for the dog in the HCA group, so last treatment carried forward ITT analyses were performed using data from 15 HCA treated and 13 placebo-treated dogs. There were otherwise no significant protocol deviations in either group.

Table 3. Owners' global evaluation score. The owners were asked to tick the box that most closely resembled their impression of treatment at each revisit

1	The treatment was very difficult to administer, very poorly tolerated by my dog and did not work at all
2	The treatment was difficult to administer, poorly tolerated by my dog and was only marginally effective
3	The treatment was reasonably straightforward to administer, reasonably tolerated by my dog and partially resolved the skin problem
4	The treatment was easy to administer, well tolerated by my dog and worked quite well
5	The treatment was very easy to administer, very well tolerated by my dog and cleared up the skin problem

Table 4. Changes in CADESI-03 following treatment with 0.0584% HCA spray or placebo

Mean (95% CI)	0.0584% HCA (n = 15)	Placebo (n = 13)	P-value (significance $P < 0.05$)
% CADESI reduction on day 14	50.5* (37.4–63.6)	24.4 (0.1–48.7)	$P = 0.05$
Dogs with ≥ 50% CADESI reduction on day 14	8/15 (53.3%)	6/13 (46.2%)	$P = 1.0$
% CADESI reduction on day 28	61.4† (48.1–74.8)	13.4 (–15.7–42.4)	$P = 0.0069$
Dogs with ≥ 50% CADESI reduction on day 28	11/15 (73.3%)	3/13 (23.1%)	$P = 0.02$

CI = confidence interval.
*Significantly decreased from baseline $P = 0.0021$.
†Significantly decreased from baseline $P = 0.0001$.

Table 5. Changes in pruritus scores (14 cm visual analogue scale) following treatment with 0.0584% HCA spray or placebo

Mean (95% CI)	0.0584% HCA (n = 15)	Placebo (n = 13)	P-value (significance $P < 0.05$)
% reduction in pruritus on day 14	26.9* (3.9–49.9)	17.6 (–62.9–27.7)	$P = 0.32$
Dogs with ≥ 50% reduction in pruritus on day 14	5/15 (33.3%)	3/13 (23.1%)	$P = 0.67$
% reduction in pruritus on day 28	38.8† (15.9–61.6)	–57.6 (–150.5–35.3)	$P = 0.0015$
Dogs with ≥ 50% reduction in pruritus on day 28	7/15 (46.7%)	1/13 (7.7%)	$P = 0.04$

CI = confidence interval.
*Not significantly decreased from baseline $P = 0.12$.
†Significantly decreased from baseline $P = 0.018$.

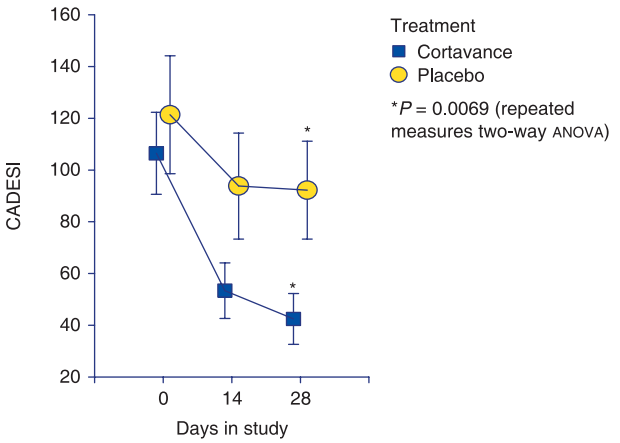

Figure 1. Mean (SD) CADESI (ITFCAD-03) during treatment with 0.0584% HCA spray (n = 15) and placebo (n = 13).

CADESI-03

The HCA-treated group exhibited a significant reduction in CADESI-03 scores throughout the trial compared to the placebo group (repeated measures ANOVA $P < 0.0001$) (Table 4 and Figure 1). There was no significant difference between groups at day 0 ($P = 0.88$). Mean CADESI-03 scores were significantly decreased compared to baseline at days 14 ($P = 0.0021$) and 28 ($P = 0.0001$) in the HCA group but not the placebo group ($P = 0.37$ and $P = 0.31$). The mean CADESI-03 score in the HCA group was significantly lower than that in the placebo group at day 28 ($P = 0.0069$) but not at day 14 ($P = 0.05$). A significantly greater number of dogs achieved a ≥ 50% reduction in CADESI-03 score following HCA treatment compared to placebo at day 28 (Fisher exact test $P = 0.02$) but not at day 14 ($P = 1.0$). There was no significant difference in the mean change in CADESI-03 between dogs with short coat (HCA: –73.6, SD 47.2; placebo: –60.4, SD 128.0) and medium/long coats (HCA: –49.6, SD 30.6; placebo: 2.4, SD = 51.4) (repeated-measures ANOVA: HCA $P = 0.3$; placebo $P = 0.64$).

Pruritus

The HCA-treated group exhibited a significant reduction in pruritus scores throughout the trial compared to the placebo group (repeated-measures ANOVA $P < 0.0001$) (Table 5 and Figure 2).There was no significant difference between groups at day 0 ($P = 1.0$). Mean pruritus scores were significantly decreased compared to baseline at day 28 ($P = 0.018$) but not at day 14 ($P = 0.12$) following the HCA spray. There was no change in the placebo group at day 14 ($P = 1.0$) or 28 ($P = 0.89$). Mean pruritus scores in the HCA group were significantly lower than those in the placebo group at day 28 ($P = 0.0015$) but not at day 14 ($P = 0.32$). A significantly greater number of dogs achieved a ≥ 50% reduction in pruritus following HCA treatment compared to placebo at day 28 (Fisher exact test $P = 0.04$) but not at day 14 ($P = 0.67$). There was no significant difference in the mean change in pruritus score between dogs with short (–3.1, SD 3.6) and medium/long coats (–2.2, SD 3.4) treated with HCA (repeated measures

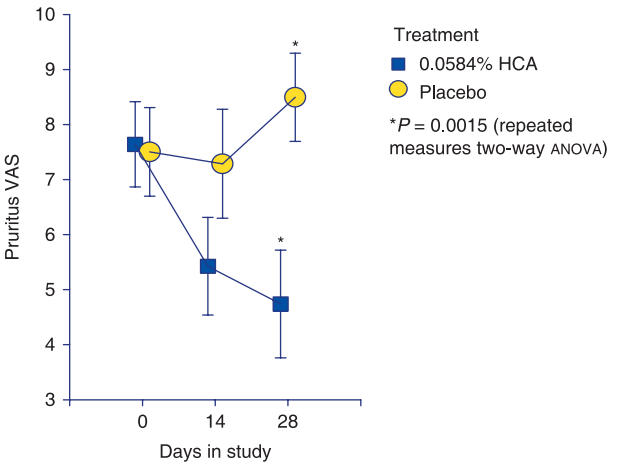

Figure 2. Mean (SD) pruritus rating (14 cm visual analogue scale [VAS]) during treatment with 0.0584% HCA spray (n = 15) and placebo (n = 13).

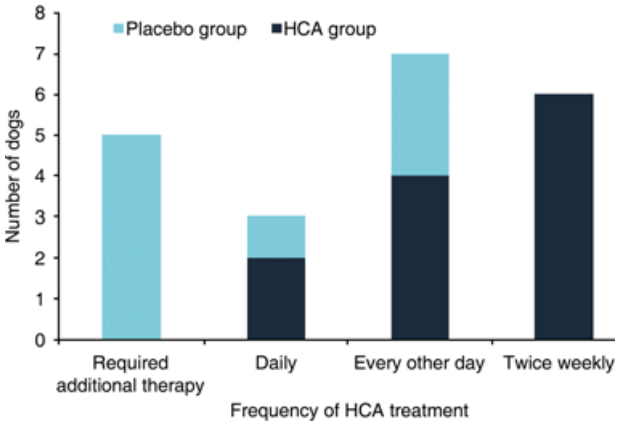

Figure 3. Maintenance treatment with 0.0584% HCA spray in 21 atopic dogs. HCA group – dogs previously treated with HCA spray in part one of the trial; Placebo group – dogs previously treated with placebo spray in part one of the trial.

Table 6. Owners' global efficacy score following treatment with 0.0584% HCA spray or placebo

Median (± SD)	Day 14	Day 28	*P*-value*
HCA spray (n = 15)	2.9 (1.2)	3.1(1.2)	$P = 0.48$
Placebo (n = 13)	2.3 (1.0)	2.4 (1.0)	$P = 0.95$
P-value*	$P = 0.0009$	$P = 0.0001$	

*Significance $P < 0.05$.

ANOVA $P = 0.63$), but there was a significant difference between short- (–3.0, SD 2.7) and medium/long-coated dogs (2, SD 3.3) in the placebo group (repeated measures ANOVA $P = 0.035$).

Owners' global efficacy score

The global efficacy score was significantly higher in the HCA treated compared to the placebo group throughout the trial (repeated measures ANOVA $P < 0.0001$). Significant differences between the two groups were seen at both days 14 ($P = 0.0009$) and 28 ($P = 0.0001$), but there were no significant differences for the scores within each group between days 14 and 28 (HCA $P = 0.48$; placebo $P = 0.95$) (Table 6). There was no difference in the owners' global efficacy score between short- (HCA = 2.7, SD 1.3; placebo = 2.4, SD 0.9) and medium/long-coated dogs (HCA: 3.1, SD 0.8; placebo: 2.1, SD 1.0) in either group (repeated measures ANOVA: HCA $P = 0.46$; placebo $P = 0.62$).

Maintenance treatment with HCA spray

Eight dogs were withdrawn during or after part one of the study at the owners' request for poor efficacy (four dogs from the placebo group) or for nontreatment related reasons (one dog from the HCA group with a possible adverse reaction [see succeeding discussion] and three other dogs from the HCA group). Of the remaining 21 dogs, three required daily therapy, seven required every other treatment and six could be maintained on twice-weekly treatment. Five dogs could not be maintained on daily HCA spray alone and required additional treatment (Figure 3). There was a significant difference in long-term control between those dogs on HCA and those on placebo in part one of the trial. Dogs originally on HCA were more likely to be maintained on every other day or twice-weekly therapy, and all of the dogs that required additional therapy had been on placebo (chi-squared test $P = 0.01$). There was no difference in the proportion of short- and medium/long-coated dogs that required daily, every other day or twice-weekly therapy maintenance therapy in either group (HCA: $P = 0.8$; placebo: $P = 0.12$).

Safety and tolerance

Both treatments were very well tolerated throughout the study. One dog was withdrawn from the HCA group after 3 days after receiving prohibited medication for severe pedal dermatitis and otitis, although it is unclear whether this was treatment related or an exacerbation of the AD. Adverse events in the HCA group were otherwise limited to short-term, self-resolving diarrhoea (two dogs), pyrexia and vomiting (one dog) and persistent oestrus (one dog). These were not thought to be related to treatment. Four dogs were withdrawn from the placebo group in part one of the trial as a result of lack of efficacy but no adverse events were reported.

There were complete on-trial blood analysis and ACTH stimulation data for nine dogs in the HCA group and seven dogs in the placebo group. The reasons for the missing data included investigator error, lack of owner consent and lost samples. There were no significant abnormalities on haematology and biochemistry. Most dogs had values within normal ranges at baseline and throughout the study. There were marginally increased neutrophil counts in seven dogs (four HCA and three placebo treated) at day 0 and two HCA dogs at day 28, elevated AP at days 0 (450 iμ/L; normal range 0–100) and 28 (370 iμ/L) in one HCA-treated dog, and mildly elevated creatinine at day 0 in four (two HCA and two placebo) dogs (126–150 μmol/L; normal range 20–110) and three (one HCA and two placebo) dogs at day 28 (120–128 μmol/L). There were no abnormalities seen at day 70 in any of the tested dogs. All tested dogs had pre- and post-ACTH cortisol levels within normal ranges throughout the study (Table 7).

Table 7. Pre- and post-ACTH serum cortisol concentrations of nine dogs treated with 0.0584% HCA spray and seven dogs treated with placebo

Mean (SD) cortisol nmol/L		HCA spray	Placebo
Day 0	Pre-ACTH	127.8 (100.5)	100.5 (49.2)
	Post-ACTH	366.9 (142.7)	331.6 (94.4)
Day 28	Pre-ACTH	124.1 (112.9)	116.0 (52.6)
	Post-ACTH	315.1 (92.0)	311.1 (39.4)
Day 70	Pre-ACTH	132.9 (89.5)	n/a
	Post-ACTH	306.2 (76.1)	n/a

n/a = not applicable.

Discussion

This study shows that the 0.0584% HCA spray is an effective and well-tolerated treatment for canine AD. Using the standard dosing regimen, the mean decrease in CADESI-03 score was 61.4% with the majority of dogs achieving ≥ 50% reduction, the point conventionally used to denote a significant clinical improvement.[16] The improvement in pruritus was less marked, with a mean reduction of 38.8%, with 7 of 15 dogs experiencing a ≥ 50% decrease. The clinical response was quite rapid, with an improvement from baseline evident by 14 days, with further improvement at 28 days. The second part of the trial demonstrated that 13 of 21 dogs could be maintained for 2–4 weeks on HCA spray alone administered every other day or less often. The owners' global efficacy ratings corroborated these results, although several owners that rated the clinical efficacy and tolerance very high found the spray difficult to apply. It would therefore be better to separate these factors into three owner scores in future trials.

The coat length did not appear to influence the response to treatment, ease of application or tolerance of the HCA spray, although pruritus scores were significantly lower in short-coated dogs treated with placebo compared to medium/long-coated dogs. The reason for this is not known, and it is possible that stratification of the data reduced group sizes and statistical power resulting in a type 1 error. The spray is formulated to penetrate the hair coat, minimizing the effect of coat length. In addition, although dogs were not preselected by lesion type or distribution, AD classically affects the less well-haired parts of the body facilitating topical treatment.

HCA was very well tolerated in this study with no adverse events attributable to treatment. This is generally a better safety profile than reported for other anti-inflammatory agents such as antihistamines, arofylline, misoprostol, cyclosporine and systemic glucocorticoids.[4,16–18] There was no clinical evidence of cutaneous atrophy or secondary infection and no significant changes to blood parameters or adrenal function following treatment for up to 70 days. This indicates that there is minimal systemic absorption of active compound following topical administration. This is in marked contrast to traditional topical glucocorticoids, which are absorbed systemically, resulting in significant local and systemic adverse effects following long-term and/or extensive application.[4,7–9] This study, however, only followed dogs for a maximum of 70 days, and as AD is usually a life-long condition, longer-term studies of safety are warranted. The assessment of cutaneous atrophy, furthermore, was subjective and did not employ more objective measures that might have detected minor changes. Recent studies using repeated histopathology, however, detected no changes in epidermal or dermal thickness, or hair follicles at treated sites in healthy dogs over three months (C. Reme, personal communication). Nevertheless, HCA is not licensed for long-term treatment, and clinicians should carefully monitor treated animals for adverse effects.

The longer-term response to HCA treatment was variable between dogs. Variation in the frequency of long-term medication has been noted for cyclosporine[19] and glucocorticoids.[4] This may be caused by inherent severity of condition, environment (e.g. allergen or irritant exposure), genotypic differences in response to drug therapy or compliance. Interesting, all five of the dogs that required additional therapy in part two of the trial received placebo in part one. This suggests that although significant clinical remission was evident by 14–28 days, continued further improvement enabled a reduction in the frequency of therapy. These results are encouraging as monotherapy is not normally recommended.[3] It is therefore possible that adjunct treatments such as skin barrier care, allergen avoidance and ASIT will permit less frequent treatment in more dogs.

There are a number of possible reasons for the discrepancy between the changes in CADESI and pruritus scores. CADESI scores have been widely used and modified over 10 years to provide objective measures of acute inflammation, chronic inflammation and self-trauma.[16,20] The CADESI-03 used in this study has been shown to have high intra- and inter-observer reliability, and is a relevant and reliable assessment of clinical severity.[15] Pruritus scores, in contrast, have not been studied or validated to the same extent. Studies have questioned the reliability and repeatability of simple VAS scores, and a combined VAS scale with behavioural descriptors was found to be superior.[21,22] It is also possible that the change in CADESI-03 score does not correlate with the change in pruritus. It includes excoriation and self-induced alopecia as measures of self-trauma, but despite this it is predominantly a dermatological assessment of cutaneous inflammation and trauma. This can be reliably and objectively assessed, but may not be as relevant to owners and therefore as good a measure of quality of life as pruritus. Limiting the assessment of pruritus to the preceding 24 h may also make this more vulnerable to short-term changes than CADESI scores. An alternative explanation for the discrepant results is that HCA has differential effects on inflammation and pruritus.

A minority of dogs appeared to respond to the placebo spray, although in contrast to the HCA treated group the 95% confidence intervals for the percentage change in both CADESI-03 and pruritus spanned 0, indicating that there was no overall benefit. One weakness of this study is that placebo controlled trials tend to over-emphasize beneficial responses to active treatments. It will therefore be interesting to compare the efficacy of 0.0584% HCA to other anti-inflammatory treatments, although the unique nature of this product will necessitate a single-blind or double-placebo trial design.

This study was carried out to good clinical practice standards.[16] Rigorous inclusion and exclusion criteria were established before the trial to ensure an unambiguous diagnosis of AD. Selection bias in breed, age, sex, weight and clinical severity was not apparent. Atopic dogs were sequentially recruited according to the inclusion and exclusion criteria, and willingness and ability of the owners to participate. They were specifically not recruited according to their spectrum or distribution of clinical signs, coat length or perceived suitability for topical treatment to ensure that they were representative of atopic dogs presented to veterinary clinics. Four random treatment identifiers (A, B, C and D) were used to minimize identification of treatment group by response, which could have influenced the assessment of dogs subsequently assigned to the same treatment. Ideally, each sequential treatment allocation should have a unique code but this proved logistically impossible given the widespread distribution of the trial sites and wide weight range of subjects (2.1–83 kg). Detection bias was otherwise unlikely as the placebo and HCA sprays were identical, and the investigators and owners remained unaware of the treatment allocation throughout the whole trial. Performance bias was also considered unlikely as there were few concomitant treatments apart from flea control, and these appeared to be distributed evenly between the groups. Attrition bias was present in both parts of the study. In part one, five dogs were lost although on-treatment data were available in four cases permitting ITT analyses. In addition to these cases three more dogs were lost prior to part two of the study. Poor efficacy was an issue in five of eight dogs (although four were on placebo in part one) and it is therefore possible that this biased towards a favourable response to treatment.

Acknowledgements

The authors are grateful for statistical support from Virbac SA and The University of Liverpool National Centre for Zoonosis Research.

References

1. Hillier A, Griffin CE. The ACVD task force on canine atopic dermatitis (I): incidence and prevalence. Veterinary Immunology and Immunopathology 2001; 81: 147–51.
2. Olivry T, DeBoer DJ, Griffin CE *et al.* The ACVD task force on canine atopic dermatitis. Forewords and lexicon. Veterinary Immunology and Immunopathology 2001; 81: 143–6.
3. Olivry T, Sousa CA. The ACVD task force on canine atopic dermatitis (XIX): general principles of therapy. Veterinary Immunology and Immunopathology 2001; 81: 311–6.
4. Olivry T, Sousa CA. The ACVD task force on canine atopic dermatitis (XX): glucocorticoid pharmacotherapy. Veterinary Immunology and Immunopathology 2001; 81: 317–22.
5. Rivierre C, Dunston SM, Olivry T. Effects of a 1 per cent hydrocortisone conditioner on the prevention of immediate and late-phase reactions in canine skin. Veterinary Record 2000; 147: 739–42.
6. DeBoer DJ, Cooley AJ. Use of induced cutaneous immediate-type hypersensitivity reactions to evaluate anti-inflammatory effects of triamcinolone topical solution in three dogs. Veterinary Dermatology 2000; 11: 25–33.
7. Kimura T, Doi K. Dorsal skin reactions of hairless dogs to topical treatment with corticosteroids. Toxicologic Pathology 1999; 27: 528–35.
8. Thomas RC, Logas D, Radosta L, Harrison J. Effects of a 1% hydrocortisone conditioner on haematological and biochemical parameters, adrenal function testing and cutaneous reactivity to histamine in normal and pruritic dogs. Veterinary Dermatology 1999; 10: 109–16.
9. Gross TL, Walder EJ, Ihrke PJ. Subepidermal bullous dermatosis due to topical corticosteroid therapy in dogs. Veterinary Dermatology 1997; 8: 127–31.
10. Brazzini B, Pimpinelli N. New and established topical corticosteroids in dermatology: clinical pharmacology and therapeutic use. American Journal of Clinical Dermatology 2002; 3: 47–58.
11. Schackert C, Korting HC, Schäfer-Korting M. Qualitative and quantitative assessment of the benefit-risk ratio of medium potency topical corticosteroids *in vitro* and *in vivo* – Characterisation of drugs with an increased benefit-risk ratio. Biodrugs 2000; 13: 267–77.
12. Ruzicka T. Methylprednisolone aceponate in eczema and other inflammatory skin disorders – a clinical update. International Journal of Clinical Practice 2006; 60: 85–92.
13. Bieber T, Vick K, Folster-Holst R *et al.* Efficacy and safety of methylprednisolone aceponate ointment 0.1% compared to tacrolimus 0.03% in children and adolescents with an acute flare of severe atopic dermatitis. Allergy 2007; 62: 184–9.
14. DeBoer DJ, Hillier A. The ACVD task force on canine atopic dermatitis (XV): fundamental concepts in clinical diagnosis. Veterinary Immunology and Immunopathology 2001; 81: 271–6.
15. Olivry T, Marsella R, Iwasaki T, Mueller R. Validation of CADESI-03, a severity scale for clinical trials enrolling dogs with atopic dermatitis. Veterinary Dermatology 2007; 18: 78–86.
16. Olivry T, Mueller RS. Evidence based veterinary dermatology: a systematic review of the pharmacotherapy of atopic dermatitis. Veterinary Dermatology 2003; 14: 121–46.
17. Marsella R, Olivry T. The ACVD task force on canine atopic dermatitis (XXII): nonsteroidal anti-inflammatory pharmacotherapy. Veterinary Immunology and Immunopathology 2001; 81: 331–45.
18. DeBoer DJ, Griffin CE. The ACVD task force on canine atopic dermatitis (XXI): antihistamine pharmacotherapy. Veterinary Immunology and Immunopathology 2001; 81: 323–9.
19. Steffan J, Parks C, Seewald W. Clinical trial evaluating the efficacy and safety of cyclosporine in dogs with atopic dermatitis. Journal of the American Veterinary Medical Association 2005; 226: 1855–63.
20. Olivry T, Guaguère E, Heripret D. Treatment of canine atopic dermatitis with misoprostol, a prostaglandin E-1 analogue: an open study. Journal of Dermatological Treatment 1997; 8: 243–7.
21. Plant JD. Repeatability and reproducibility of numerical rating scales and visual analogue scales for canine pruritus severity scoring. Veterinary Dermatology 2007; 18: 190–1.
22. Hill PB, Lau P, Rybnicek J. Development of an owner-assessed scale to measure the severity of pruritus in dogs. Veterinary Dermatology 2007; 18: 301–8.

Résumé Cette étude a évalue un spray de 0.0584% hydrocortisone aceponate (HCA) (Cortavance®; Virbac SA, Carros, France) dans la dermatite atopique canine (AD). Initialement, les chiens avec un score canine atopic dermatitis extent and severity index [CADESI-03] ≥ 50 étaient au hasard traités soir avec HCA (n = 15) soit avec un placebo (n = 13) (deux sprays à 10 cm de la zone à traiter pour 100 cm^2) une fois par jour pendant 28 jours. Vingt et un des chiens ont ensuite reçu le spray HCA une fois par jour, en diminuant à tous les deux jours ou deux fois par semaine sur 42 jours si l'amélioration était maintenue. CADESI, prurit (14 cm

échelle analogique visuelle) et satisfaction des propriétaires (échelle de 5-points) étaient les critères retenus tous les 14 jours. Une Hématologie, une biochimie et un test de stimulation à l'ACTH étaient réalisés à l'inclusion à d28 et d70 (HCA $n = 9$; placebo $n = 7$). Les données ont été analysées en intention de traiter. Le spray HCA a significativement diminué le CADESI (–61.4% *versus* –13.4%, $P = 0.0069$) et le prurit (–38.8% *versus* +57.6%, $P = 0.0015$) à d28 en comparaison avec le placebo. Les scores étaient significativement diminués à d14 (CADESI –50.5%, $P < 0.0021$) et d28 (CADESI $P < 0.0001$; pruritus $P = 0.018$) en comparaison avec l'inclusion après le HCA mais pas le placebo. A d28 11/15 et 7/15 chiens du groupe HCA avaient ≥ 50% de réduction du CADESI et du prurit en comparaison de 3/13 ($P = 0.02$) et 1/13 ($P = 0.04$) du groupe placebo. Les scores de satisfaction des propriétaires étaient significativement plus élevés dans le groupe HCA (d28 $P = 0.0001$). un traitement quotidien a été nécessaire pour 3/21 chiens, 7/21 un jour sur deux, 6/21 deux fois par semaine et 5/21 chiens ont eu besoin de traitements additionnels. La longueur du poil n'a pas influencé les résultats. Aucun effet secondaire ou anomalie des paramètres sanguins n'a été observée. Le spray HCA s'est avéré sûr et efficace jusqu'à 70 jours d'application. Il n'est toutefois pas commercialisé pour des traitements au long cours.

Resumen Este estudio evaluó un pulverizado de 0.0584% de aceponato de hidrocortisona (HCA) (Cortavance®; Virbac SA, Carros, France) en dermatitis atópica canina (AD). Inicialmente los perros con un índice de extensión y severidad de dermatitis atópica canina [CADESI-03] ≥ 50 fueron distribuidos al azar para recibir HCA ($n = 15$) o placebo ($n = 13$) (dos pulverizados a 10 cm de distancia para tratar un área de 100 cm^2) una vez al día durante 28 días. Veintiuno de los perros recibieron entonces pulverizado HCA una vez al día, reduciendo a días alternos o dos veces en semana a lo largo de 42 días si se mantenía la mejora. Cada 14 días se anotaron el CADESI, prurito (escala visual análoga a 14 cm) y satisfaccion de los propietarios (escala de cinco puntos). Se realizarion análisis hematológicos y bioquímicos y prueba de estimulación de ACTH al inicio, en los días 28 y 70 (HCA $n = 9$; placebo $n = 7$). Los datos de intencion de tratar tambien fueron analizados. El pulverizado de HCA disminuyó significativamente CADESI (–61.4% frente a –13.4%, $P = 0.0069$) y prurito (–38.8% frente a +57.6%, $P = 0.0015$) al día 28 comparado con el placebo. Las valores fueron significativamente menores al día 14 (CADESI –50.5%, $P < 0.0021$) y día 28 (CADESI $P < 0.0001$; prurito $P = 0.018$) comparados con valores iniciales tras HCA pero no placebo. En el día 28 11/15 y 7/15 perros tratados con HCA dogs tenían una reducción ≥ 50% en CADESI y prurito comparado con 3/13 ($P = 0.02$) y 1/13 ($P = 0.04$) perros tratados con placebo. Los valores de satisfacción del propietario fueron mayores en el grupo tratado con HCA (d28 $P = 0.0001$). Un tratamiento diario de mantenimiento fue necesario en 3/21 perros, 7/21 en días alternos, 6/21 dos veces en semana y 5/21 necesitaron tratamiento adicional. La longitud del pelo no influyó en los resultados. No se obsevaron efectos adversos ni cambios en los valores sanguíneos. El pulverizado de HCA probó ser seguro y efectivo hasta los 70 días. Sin embargo no está autorizado para tratamientos a largo plazo.

Zusammenfassung In dieser Studie wurde ein 0.0584%iger Hydrocortison Aceponat (HCA) Spray (Cortavance®; Virbac SA, Carros, France) für die canine atopische Dermatitis (AD) evaluiert. Anfangs wurden Hunde mit einem Caninen Atopischen Dermatitis Extent and Severity Index [CADESI-03] ≥ 50 zufällig eingeteilt, um HCA ($n = 15$) oder Plazebo ($n = 13$) (beides Sprays, um aus 10 cm Entfernung eine Fläche von 100 cm^2 zu behandeln) einmal täglich 28 Tage lang zu erhalten. Einundzwanzig der Hunde erhielten den HCA Spray einmal täglich, was auf jeden zweiten Tag oder auf zweimal wöchentlich im Verlauf von 42 Tagen reduziert wurde, wenn eine Verbesserung bestehen blieb. CADESI, Juckreiz (14 cm visuell-analoge Skala) und BesitzerInnen Zufriedenheit (5 Punkte Skala) wurden alle 14 Tage festgehalten. Hämatologie, biochemische Untersuchungen und ACTH Stimulation wurden am Beginn, am d28 und d70 (HCA $n = 9$; Plazebo $n = 7$) durchgeführt. Eine Intention-to-treat Analyse wurde durchgeführt. Der HCA Spray verminderte den CADESI (–61.4% *versus* –13.4%, $P = 0.0069$) und den Juckreiz (–38.8% *versus* +57.6%, $P = 0.0015$) am d28 im Vergleich zu Plazebo. Am d14 waren die Werte (CADESI –50.5%, $P < 0.0021$) und am d28 (CADESI $P < 0.0001$; Juckreiz $P = 0.018$) im Vergleich zu den Ausgangswerten nach HCA aber nicht nach Plazebo Verabreichung signifikant erniedrigt. Am d28 hatten 11/15 und 7/15 HCA Hunden eine ≥ 50% ige Reduktion des CADESI und Juckreiz Wertes im Vergleich zu 3/13 ($P = 0.02$) und 1/13 ($P = 0.04$) Plazebo Hunden. Die Werte der BesitzerInnen Zufriedenheit waren in der HCA Gruppe (d28 $P = 0.0001$) signifikant höher. Eine tägliche Erhaltungstherapie war für 3/21 Hunden, jeden zweiten Tag für 7/21 Hunden, zweimal wöchentlich für 6/21 Hunden notwendig und 5/21 Hunden benötigten eine zusätzliche Therapie. Die Länge des Fells beeinflusste die Ergebnisse nicht. Es wurden keine Nebenwirkungen oder Veränderungen der Blutparameter festgestellt. Der HCA Spray zeigte sich als sicher und effektiv bei einer Verabreichung für bis zu 70 Tage. Es ist jedoch nicht für eine Langzeittherapie lizenziert.

