

SHORT COMMUNICATIONS

Influence of food intake on the clinical response to cyclosporin A in canine atopic dermatitis

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CYCLOSPORIN A (CsA) (Atopica, Atopis soft capsules; Novartis Animal Health) was introduced recently as an oral microemulsion formulation for the treatment of dogs with atopic dermatitis. Several randomised, controlled and open clinical studies have proven its clinical efficacy (Olivry and others 2002, Steffan and others 2003, 2004). Based on pharmacokinetic data, administration of CsA is recommended two hours before or after feeding, as its bioavailability decreases and the variability of individual blood concentrations increases when the drug is given with food (Steffan and others 2004). Dosing fasted dogs is therefore recommended to optimise the drug's bioavailability. However, the clinical response of dogs after dosing with or without food has never been evaluated. This short communication describes a study to determine whether the administration of CsA with or without food could influence the clinical response in dogs with atopic dermatitis.

Twenty-five dogs with non-seasonal atopic dermatitis, diagnosed by Prélud's criteria (Prélud and others 1998) and by exclusion of differential diagnoses, were included in a multicentre, randomised study involving seven investigators in Germany. All the dogs received approximately 5 mg/kg/day CsA. The animals were randomly and sequentially divided into two groups by the lead investigator, independent of the study centre, alternating between group 1 and 2. As the various centres included dogs at different time points, the number of dogs in each group was not identical at each centre. The 15 dogs in group 1 received CsA with a meal, while the 10 dogs in group 2 were given the drug at least two hours before or after feeding. Dogs were evaluated before treatment and monthly for six months thereafter. A dose tapering regimen was applied, as described by Steffan and others (2003). The canine atopic dermatitis extent and severity index (CADESI), with scores of 0 to 3 for erythema, lichenification and excoriation at 40 different body sites, was used by the clinician at each centre, as previously described by Olivry and others (2002); pruritus was evaluated by the owner, using a visual analogue scale from 0 to 100. If the CADESI score increased above baseline, the dog was excluded from the study. If the CADESI score at any given visit was reduced by more than 50 per cent and the pruritus was adequately controlled, administration of CsA was reduced to every second day of treatment. If the CADESI score had improved by more than 75 per cent from baseline and pruritus was well controlled, the drug was administered twice weekly. If, on subsequent visits, the CADESI scores or pruritus increased, the frequency of administration was increased again to the previous level.

During a selection period of four weeks, all the dogs were treated with a long-lasting flea adulticide spot-on formulation such as selamectin, imidacloprid, fipronil or permethrin. Fipronil was used monthly during the study. Systemic antibiotics and antifungal drugs were administered as required for the treatment of secondary infections. Antipruritic drugs had to be withdrawn before inclusion in the study (CsA for eight weeks, injectable glucocorticoids for four weeks, oral/topical glucocorticoids for one week and allergen-specific immunotherapy for two weeks). Fatty acid supplementation

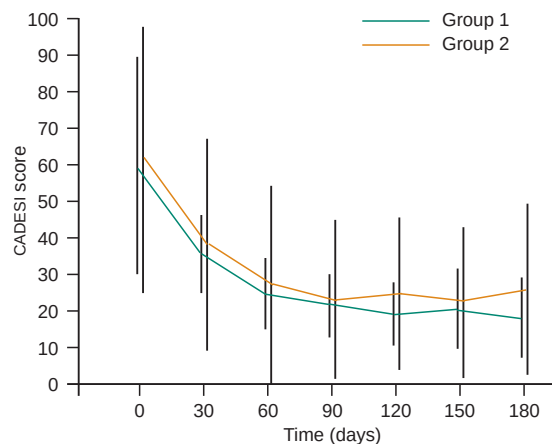


FIG 1: Mean (sd) canine atopic dermatitis extent and severity index (CADESI) scores of dogs with atopic dermatitis treated with cyclosporin A for six months, given either with food (group 1) or two hours before or after food (group 2)

or vitamin E had to be withdrawn one week before inclusion or continued for the study duration of six months. Drugs without antipruritic action and without interference with the pharmacokinetics of CsA, as well as shampoos and antibiotics, were permitted provided they were used for no longer than three periods of two weeks during the trial. All enrolled animals were included for statistical analysis (intent to treat [ITT] analysis). Missing values from visits or assessments were imputed by the 'LOCF' (last observation carried forward) method. For nominal variables (such as breed), a comparison between groups was performed using a Mantel-Haenszel general association test; for ordinal variables (such as weight), groups were compared by using a Kruskal-Wallis test. Changes relative to baseline of the CADESI or pruritus scores were evaluated with a Wilcoxon paired-samples test. A square root transformation (power with an exponent of 1/2) was performed for CADESI values, as repeated measures analysis of variance comparing groups revealed that values were not normally distributed. Differences between groups were considered significant for $P < 0.05$.

Six dogs, three in each group, did not complete the study. In three of these cases, owner compliance was insufficient; in the other three, adverse events interrupted treatment. All dogs were retained for the ITT analysis. There was no significant difference between the two groups with regard to the dogs' weight, sex, breed and disease severity at the start of the trial.

The mean starting dose was similar in the two groups (5.23 and 5.19 mg/kg in groups 1 and 2, respectively), and could be tapered down in each group with a similar timing and frequency. There was no significant difference between the groups at any time points with regard to treatment regimen. In group 1, the dose of CsA could be decreased to every other day administration in five dogs. In group 2, one dog received the drug every other day. Twice weekly administration was achieved in an additional four dogs in each group. There was no significant difference between the groups regarding the dosing regimen ($P = 0.354$).

The CADESI scores (Fig 1) decreased significantly in both groups from baseline to the first and all subsequent visits ($P < 0.0001$ and $P < 0.01$ for difference to baseline in groups 1 and 2, respectively). The pruritus scores (Fig 2) showed a similar decrease and were significantly different from baseline values at all time points ($P \leq 0.0001$ and $P < 0.01$ in groups 1 and 2, respectively, with the exception of the three-month visit [$P = 0.0156$ in both groups]). With repeated measures analysis, there was no significant difference between the two groups during the study with regard to CADESI and pruritus scores. The improvement of lesions and pruritus of more than 50 and 90 per cent by the end of the trial is shown in Table 1.

When asked for a global assessment of efficacy at the end of the study, five owners of dogs in group 1 (CsA administered

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FIG 2: Mean (sd) visual analogue scale (VAS) score, from 0 to 100, for pruritus in dogs with atopic dermatitis treated with cyclosporin A for six months, given either with food (group 1) or two hours before or after food (group 2)

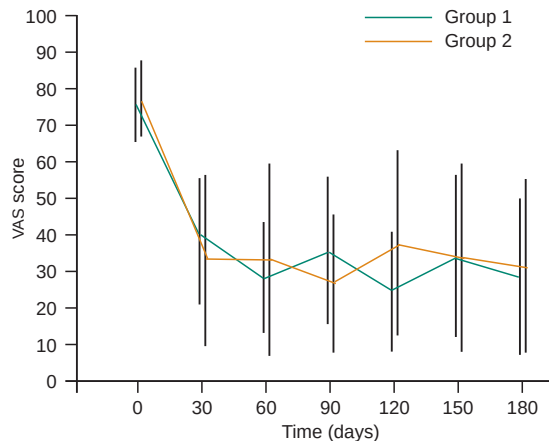


TABLE 1: Number of dogs with a reduction in atopic dermatitis of more than 50 per cent or more than 90 per cent at the end of six months' treatment out of 15 dogs that received cyclosporin A (CsA) (group 1) with food and in the 10 dogs that received CsA two hours before or after food (group 2)

Improvement	Group 1 n (%)	Group 2 n (%)
>50 per cent		
CADESI scores	13 (86.7)	7 (70)
Pruritus scores*	11 (73.3)	6 (60)
>90 per cent		
CADESI scores	1 (6.7)	1 (10)
Pruritus scores*	5 (33.3)	2 (20)

* Assessed by the owner

CADESI Canine atopic dermatitis extent and severity index

with food) judged the response to be excellent, three good and one fair. Three owners of dogs in group 2 judged the response to be excellent, two good and one fair. According to the owners, a poor response was seen in one case in each group. No response was available in five cases in group 1 and one case in group 2. There was no statistically significant difference in the global assessment between the two groups.

Gastrointestinal adverse events were recorded with a similar frequency in the two groups (six dogs had at least one event during the study in group 1, as did four dogs in group 2). In one case in group 1, treatment was interrupted because of severe colitis. Two additional dogs did not complete the trial due to adverse effects: one dog in group 1 had severe pruritus, the other, in group 2, showed neurological signs.

Steffan and others 2004 reported that the mean bioavailability of a microemulsion of CsA was reduced by 22 per cent when administered to dogs with food, while the individual variability increased. Since no correlation between clinical response and CsA blood concentration in dogs with atopic dermatitis or perianal fistulas could be demonstrated (Steffan and others 2004, Mathews and Sukhiani 1997), the clinical significance of such findings was unclear. The aim of this randomised study was therefore to compare the clinical responses in dogs affected by atopic dermatitis, after the administration of CsA with or without food, to evaluate the influence of feeding on treatment outcome. The results of the study showed no statistically significant difference in clinical efficacy between dogs that received CsA with food ('fed' dogs) or two hours before or after food ('fasted' dogs): CADESI and pruritus scores decreased in both groups from baseline to the first and all subsequent visits, and no difference could be demonstrated between the two groups at any given point.

The comparable clinical response between fasted and fed dogs may be explained by the fact that the drug concentration exceeds a threshold to meet optimum efficacy. The lack of correlation between CsA blood concentrations and efficacy parameters (Steffan and others 2004) supports this hypothesis. The active compound may reach the target tissue in a sufficient concentration to alleviate the clinical signs of atopic dermatitis, even with the lower blood levels associated with the administration with food. The effect of the feeding regimen on pharmacokinetics has only been evaluated after single, not repeated, administration. It is possible that the mean blood concentrations are similar in fed and fasted dogs after repeated dosing. In individual dogs, drug absorption may vary from day to day, so that low absorption on one day may be balanced by higher absorption the next day, resulting

in similar mean drug concentrations at steady state in fed and fasted dogs.

In approximately 50 to 60 per cent of dogs in this study, the dose of CsA could be decreased successfully to every other day or twice weekly administration. This concurs with the results of a previous meta-analysis (Steffan and others 2006).

In the present study, as in previous studies (Olivry and others 2002, Steffan and others 2003), intermittent vomiting and diarrhoea were the most frequent adverse events at the beginning of treatment. The frequency of these events was similar in fed and fasted dogs. These results suggest a limited effect of feeding on the incidence of gastrointestinal adverse events. Due to the limited number of animals, further studies are needed to evaluate the influence of mode of administration on the rate of gastrointestinal side effects.

Cessation of therapy was required in three dogs: one dog in group 1 had recurrent diarrhoea, one in group 1 had severe pruritus, and one in group 2 was excluded from the study after displaying neurological signs. Three additional dogs did not complete the study because of compliance problems. Overall, the safety of the drug did not appear to be influenced by the feeding regimen.

This small-scale study, which aimed to explore the influence of the feeding regimen on the efficacy and safety profile of the microemulsion formulation of CsA, suggests that the administration of CsA with food does not influence the clinical response or the frequency of adverse events.

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