Cyclosporine A in Felines: Is blood monitoring of value?

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Introduction

Cyclosporine A[1] (CsA) is a powerful immunosuppressant that is being increasingly used to treat allergies and other immune-mediated diseases in veterinary medicine. Only limited information on the safe use of CsA is available in cats. Case studies (*e.g.* Heinrich *et al*., 2011) have reported vomiting and diarrhoea as frequent adverse events (AEs). As part of the clinical safety assessment of CsA for the treatment of feline allergic dermatitis (FeLAD), investigations have been conducted in male and female cats of various breeds (age range: 1 to 16 years) from multi-centre field studies. Blood samples were collected to investigate if CsA exposure was indicative of gastrointestinal (GI) disorders and associated with significant changes in blood chemistry parameters (albumin, alanine aminotransferase (ALT), glucose, and creatinine). In a first study [A], cats were treated with a placebo control (n: 35) or CsA at 2.5 or 7.0 mg/kg (n: 32 and n: 33, respectively) for several weeks to set the effective dose of CsA. This preliminary investigation was followed by a field efficacy and tolerability study [B] where 218 cats received CsA at a target dose of 7 mg/kg daily (n: 145) or a placebo control (n: 73).

[1] Atopica®, Novartis Animal Health, Basel, Switzerland.

Problem list

- Use of cyclosporine A in feline allergic dermatitis
- Cyclosporine A monitoring strategies in dermatology
- Are cyclosporine A concentrations in blood indicative of gastrointestinal disorders?
- Are repeated administrations of cyclosporine A associated with significant changes in clinical chemistry?

Use of cyclosporine A in feline allergic dermatitis

Allergic dermatitis is a pretty common disease in cats characterized by pruritus and varying degrees of alopecia, erythema and crusting (Scott *et al*., 2001). Lesions can be found on the neck, forelegs, thorax and caudal thighs. Contrary to dogs, there is no defined phenotype for what an atopic cat should look like and it is often difficult to establish a definite diagnosis of FeLAD. In essence, this condition should be regarded as a diagnosis of exclusion, when flee allergy dermatitis and food intolerance have been discarded. Management of FeLAD relies on oral administrations of anti-inflammatory doses of corticosteroids, though the relatively high prevalence of AEs associated with this therapy (*e.g.* polyuria, polydipsia, polyphagia, vomiting and loose stool) has encouraged the use of alternative treatments (*e.g.* CsA). In veterinary medicine CsA is available as a microemulsion in soft gelatin capsules of 10, 25, 50 and 100 mg. In a study by Noli & Scarampella (2006), a cohort of cats with signs of allergic skin disease were administered CsA at a daily dose of 3.6 to 8.3 mg/kg for one month. Good or excellent improvement was observed in more than 50% of cats with a substantial decrease in mean lesion scores. Another study by Wisselink & Willemse (2009) from the University of Utrecht has reported no significant differences in terms of remission or clinical improvement between prednisolone and CsA treated cats. No serious side effects were observed either. The authors concluded that CsA was an effective alternative to prednisolone therapy in cats with presumed allergic dermatitis.

Cyclosporine A monitoring in dermatology

Monitoring of CsA blood levels following organ transplantation has been established as a routine practice in human patients. Unlike its use in organ transplants the value of blood monitoring in predicting toxicity or efficacy in skin diseases remains unclear. Investigations in canine patients have shown that GI disorders occurred more

frequently at higher CsA doses and higher trough concentrations (Scott *et al*., 2001). Monitoring of blood concentrations was recommended by one pharmacokinetic study in healthy dogs reporting substantial between-subject variability in the maximum concentrations of CsA (Daigle *et al*., 2000). Because of its known interaction with CsA metabolism, patient monitoring is also recommended when ketoconazole therapy has been initiated. In most cases though, monitoring of blood levels in dogs is not predictive of prevalence of AEs or clinical efficacy. The consensus of a roundtable of dermatologists on the treatment of canine atopic dermatitis recommended dosing of CsA based on clinical information, not blood concentrations (Rosenbaum, 1999). In human patients treated with CsA for one week, skin concentrations were 10 times higher than trough blood samples, indicating that measurement of CsA in blood may not be relevant in dermatologic diseases (Wong *et al*., 1993). To date, only limited information on the safe use of CsA is available in cats, even less is known about monitoring of blood levels. Data from 50 cats with allergic dermatitis have recently shown that AEs occurred in 66% of cats receiving CsA (Heinrich *et al*., 2011). Most of AEs were GI in nature (vomiting and diarrhoea in 25% and 15% of cases, respectively).

Are cyclosporine A concentrations in blood indicative of gastrointestinal disorders?

Vomiting and diarrhoea events, as assessed by cat owners, were reported throughout the length of studies A and B. Blood samples were collected at the end of both studies, after prolonged oral administration of CsA. Cyclosporine concentrations in blood were determined by mass spectrometry. Individual pharmacokinetics parameters were derived using a nonlinear mixed effect model. Parameter estimates of apparent clearance were used to compute CsA exposure at steady state as follows:

$$AUCss_i = Dose_i / (CL/F)_i$$

Where **$AUCss_i$** is the predicted **area under the curve of CsA blood concentrations** for the i^{th} individual, and **$(CL/F)_i$** is the **apparent clearance** for this individual.

$AUCss_i$ estimates were finally compared between individuals with and without GI disorders using parametric (Student test) and nonparametric (Wilcoxon rank sum test) statistical methods. Two-tailed p-values < 0.05 were considered as significant.

As highlighted in Figure 1, no significant difference in exposure was observed between vomiting and non-vomiting cats, indicating that emesis was not related to CsA exposure (difference of 11% with p-value: 0.43 and 0.57 for Wilcoxon rank sum test and Student test, respectively). Unlike vomiting, diarrhoea episodes were likely to be associated with higher CsA exposure (see right-hand side of Figure 1) (difference of 31% with p-value: 0.042 and 0.123 for Wilcoxon rank sum test and Student test, respectively). Parallel to diarrhoea a slight reduction in body weight (< 5%) was reported in CsA treated cats (see Figure 2). The specific cause of CsA-associated GI events in cats is unknown, but these data support the hypothesis that diarrhoea is exposure (and thereby dose) related in cats.

Are repeated administrations of cyclosporine A associated with significant changes in clinical chemistry?

Though information on the toxicity of CsA is limited to few case studies in cats, the safety profile of CsA is now well documented in dogs and human patients. The liver, kidneys and pancreas are known target organs of CsA toxicity that were monitored in the present studies. Changes in blood chemistry parameters were compared between treatment groups using nonparametric (Wilcoxon rank sum test) statistical methods. Two-tailed p-values < 0.05 were considered as significant.

Liver toxicity

Liver injury (as indicated by an increase in ALT and a decrease in albumin plasma levels) is a common side effect of CsA therapy in human patients. Data from *in vitro* experiments in perfused rat liver and isolated mitochondria have shown that chronic CsA treatment can cause a hypermetabolic state leading to hypoxia and liver injury (Zhong *et al*., 2001).

As indicated in Figure 3, CsA treated cats did not experience an increase in ALT when compared to baseline values. Unlike ALT, a moderate reduction (*ca.* 10%) in albumin levels was observed in the 2.5 mg/kg dose group (p-value: 0.0028), though albumin concentrations remained within the range of physiological values (see Figure 4). This variation was not considered as clinically significant. In addition, no substantial changes were reported in the 7.0 mg/kg dose group.

Renal toxicity

Prolonged treatment with CsA is also associated with chronic renal damage in humans (as suggested by an increase in creatinine plasma levels). Studies in dogs (*e.g.* Fisch *et al*., 1993) only showed moderate kidney toxicity, with no changes in renal clearance even at high CsA doses (20-30mg/kg).

As presented in Figure 5, only a modest increase (*ca.* 12%) in creatinine was observed in the 7.0 mg/kg dose group (p-value < 0.001). This change was not considered as clinically significant. Plasma levels remained within the range of physiological values. No obvious changes were reported in the 2.5 mg/kg dose group.

Inhibition of insulin secretion

Cyclosporine A has been shown to inhibit insulin secretion in *in vitro* tests and *in vivo* glucose-stimulation studies. In target animal safety studies CsA treated dogs remained nonetheless normoglycaemic (Steffan *et al*., 2003).

Similar to creatinine, an increase (*ca.* 18%) in glucose was observed in the 7.0 mg/kg dose group (p-value < 0.001) (See Figure 6). This change was not considered as clinically significant. Plasma levels remained within the range of physiological values. No obvious changes were reported in the 2.5 mg/kg dose group.

Conclusions

Cyclosporine treatment appears to be well tolerated in cats when used for the control of allergic dermatitis. However, the data also suggest that establishing the lowest effective clinical dose regimen (*i.e.* between 2.5 and 7.0 mg/kg) will improve the drug's safety profile. CsA exposure in blood was not found to be a predictor of safety at the recommended doses of Atopica®. In addition, as CsA is known to be immunosuppressive, animals with significant systemic disease including neoplasia or serious infectious disease should not receive CsA for the control of allergic skin disease. Monitoring of body weight is recommended.

References

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Figure 1: Area under the curve of steady state (AUCss in ng/mL.h^{-1}) cyclosporine A (CsA) concentrations of cats with ("Yes") and without ("No") gastrointestinal disorders (25th, 50th and 75th percentiles). Vertical bars indicate +/- one standard deviation. Left-hand side: vomiting events, right-hand side: diarrhea episodes. In [A] (dose ranging study), cats were treated with a placebo control (n: 35) or CsA at 2.5 or 7.0 mg/kg (n: 32 and n: 33, respectively) for up to six weeks. In [B] (efficacy and tolerability study) 218 cats received CsA at a target dose of 7 mg/kg daily (n: 145) or a placebo control (n: 73).

No significant difference in exposure was observed between vomiting and non-vomiting cats, indicating that emesis was not related to CsA exposure (p-value: 0.43 and 0.57 for Wilcoxon rank sum test and Student test, respectively). Unlike vomiting, diarrhea episodes were likely to be associated with higher CsA exposure (p-value: 0.042 and 0.123 for Wilcoxon rank sum test and Student test, respectively).

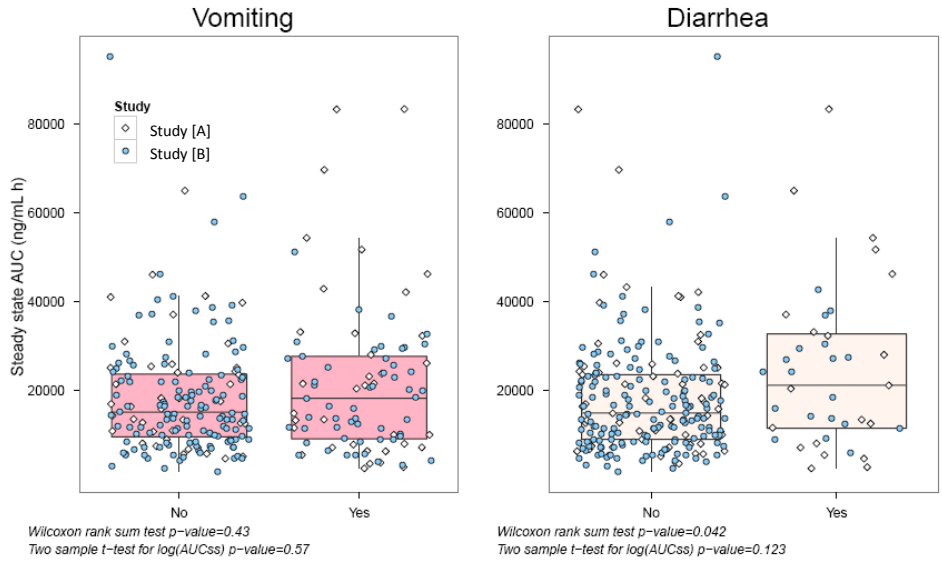

Figure 2: Body weight change from baseline (%) in cyclosporine A (CsA) treated cats. Red dots: individual values, grey dotted lines: interpolation within each individual, blue continuous line: average value.

Only a slight and not significant reduction in body weight (< 5%) was observed after repeated oral administrations of CsA.

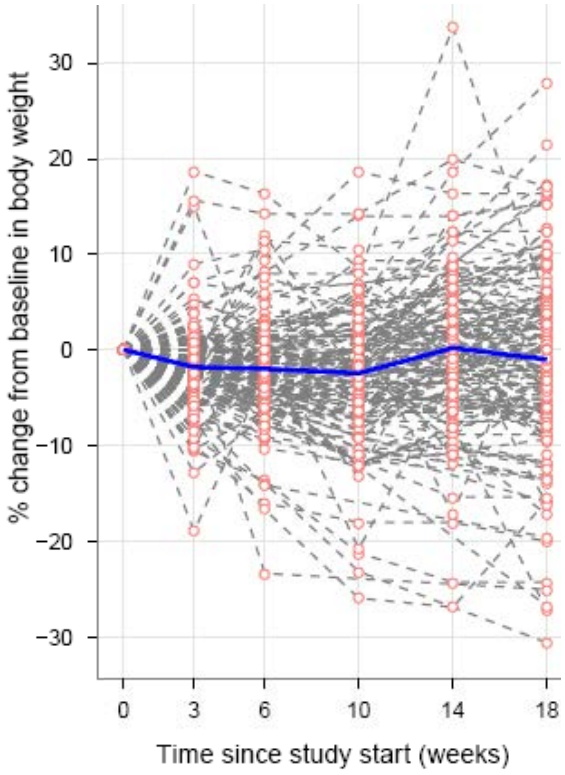

Figure 3: Alanine aminotransferase (ALT) levels (IU/L) before (baseline) and after repeated administrations of a placebo control or cyclosporine A at a daily dose of 2.5 and 7.0 mg/kg (25th, 50th and 75th percentiles). Vertical bars indicate +/- one standard deviation. Information on ALT from the 2.5 mg/kg group was only documented in study [A]. Details on study design can be found in the legend of Figure 1.

Cyclosporine treated cats did not experience an increase in ALT when compared to baseline values.

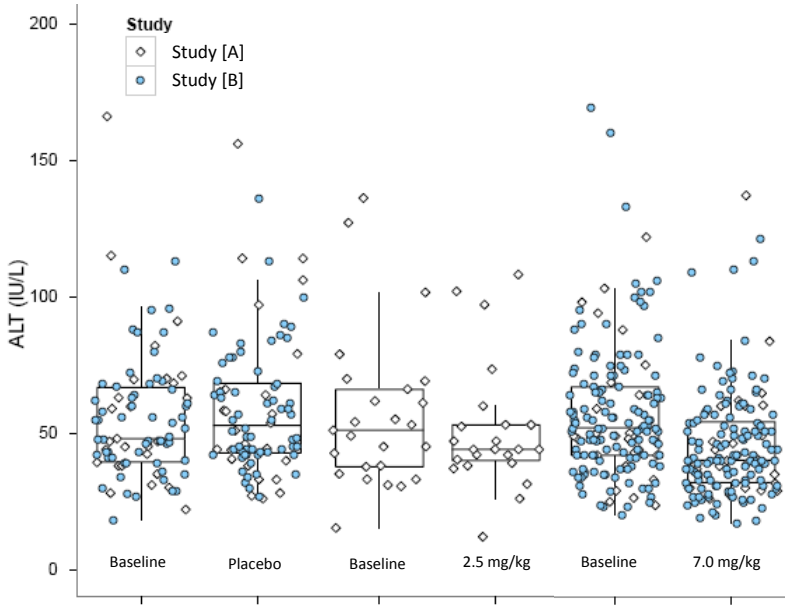

Figure 4: Albumin concentrations (g/L) before (baseline) and after repeated administrations of a placebo control or cyclosporine A at a daily dose of 2.5 and 7.0 mg/kg (25th, 50th and 75th percentiles). Vertical bars indicate +/- one standard deviation. **: 0.001 < p-value < 0.01. Information on albumin from the 2.5 mg/kg group was only documented in study [A]. Details on study design can be found in the legend of Figure 1.

A moderate reduction (*ca.* 10%) in albumin levels was observed in the 2.5 mg/kg dose group (p-value: 0.0028), though albumin concentrations remained within the range of physiological values. This variation was not considered as clinically significant. In addition, no substantial changes were reported in the 7.0 mg/kg dose group.

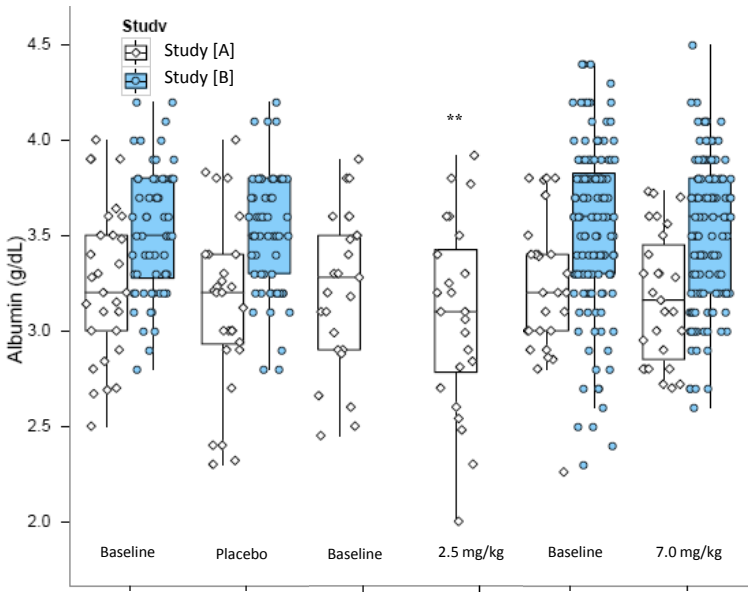

Figure 5: Creatinine concentrations (mg/dL) before (baseline) and after repeated administrations of a placebo control or cyclosporine A at a daily dose of 2.5 and 7.0 mg/kg (25th, 50th and 75th percentiles). Vertical bars indicate +/- one standard deviation. ***: p-value < 0.001. Information on creatinine from the 2.5 mg/kg group was only documented in study [A]. Details on study design can be found in the legend of Figure 1.

Only a modest increase (*ca.* 12%) in creatinine was observed in the 7.0 mg/kg dose group. This change was not considered as clinically significant. Plasma levels remained within the range of physiological values. No obvious changes were reported in the 2.5 mg/kg dose group.

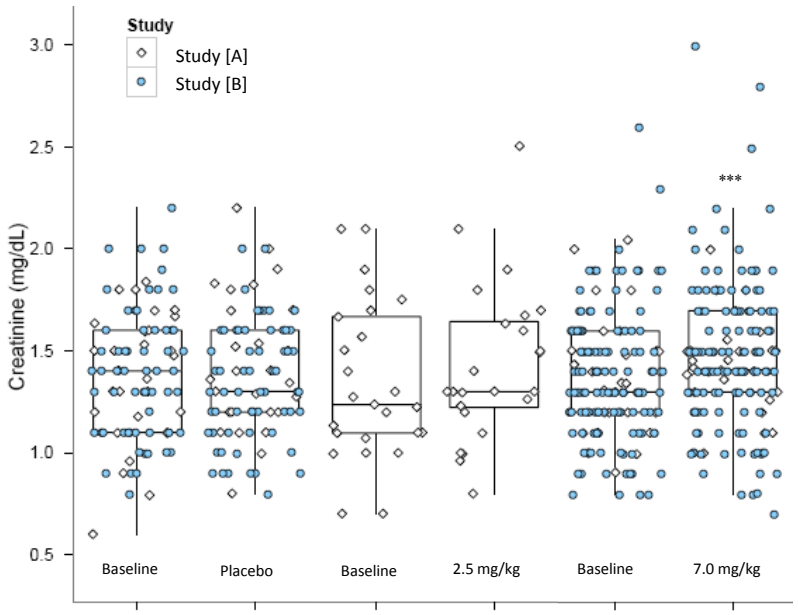

Figure 6: Glucose concentrations (mg/dL) before (baseline) and after repeated administrations of a placebo control or cyclosporine A at a daily dose of 2.5 and 7.0 mg/kg (25th, 50th and 75th percentiles). Vertical bars indicate +/- one standard deviation. ***: p-value < 0.001. Information on glucose from the 2.5 mg/kg group was only documented in study [A]. Details on study design can be found in the legend of Figure 1.

Similar to creatinine, an increase (*ca.* 18%) in glucose was observed in the 7.0 mg/kg dose group. This change was not considered as clinically significant. Plasma levels remained within the range of physiological values. No obvious changes were reported in the 2.5 mg/kg dose group.