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**PHARMACOKINETICS AND CLINICAL EFFICACY OF CYCLOSPORINE
TREATMENT IN DOGS WITH STEROID RESISTANT INFLAMMATORY
BOWEL DISEASE**

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The mainstay of therapy for dogs with inflammatory bowel disease (IBD) is immunosuppressive doses of corticosteroids. Some dogs are resistant to treatment and present a substantial challenge to the clinician. In humans cyclosporine A (CSA) has been shown to be effective in treating steroid refractory attacks of IBD. CSA is an immunosuppressive agent acting through inhibition of IL-2 production which reduces lymphocyte activation and antibody production. The purpose of this study was to assess the clinical efficacy of oral CSA treatment as well as the pharmacokinetics in dogs with steroid-resistant IBD.

Fourteen dogs with IBD that had been treated a minimum of 10 weeks with immunosuppressive doses of corticosteroids were prospectively enrolled in the study. Diagnosis of IBD was through intestinal biopsy with thorough ancillary testing ruling out secondary disorders. The dogs were treated with modified CSA (Atopica®) at 5 mg/kg PO once daily for 10 weeks. A score was used to grade the severity of clinical signs before and after treatment using the canine IBD activity index (CIBDAI). In 9 dogs an endoscopy was performed to harvest duodenal and gastric biopsy samples to evaluate histologic changes after treatment. In seven dogs whole blood EDTA samples were obtained immediately before and 1, 2, 4, 8 and 24 hours after the first dose of CSA. Samples were tested for CSA levels using a polarization immunoassay.

Significant improvement in clinical signs based on the CIBDAI was seen in 12 of 14 dogs. A statistically significant increase in body weight was also noted in those dogs showing clinical improvement. In the 9 dogs with repeat endoscopy there was no difference in grade of histological changes before and after CSA treatment.

Pharmacokinetic assessment of CSA showed a mean peak level of 765 ng/ml at an average of 1.57 hours and a mean trough level of 37 ng/ml. These levels are similar to those in normal dogs administered oral CSA. Transient adverse effects that were noted included; vomiting or anorexia (4/12), gingival hyperplasia (1/12) and hair loss (1/12).

This study shows that CSA is a valuable treatment alternative in dogs with steroid refractory IBD. It also appears CSA pharmacokinetics are similar in dogs with IBD compared to normal dogs. The dosage used and the trough level attained is lower than the therapeutic levels suggested for immunosuppression in humans. An interesting finding which has been suggested in previous studies was the lack of reduction in severity of histological findings.

USE OF COMPOUNDED ACTH FOR ADRENAL FUNCTION TESTING IN DOGS

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ACTH stimulation testing is used for diagnosis of hyperadrenocorticism and hypoadrenocorticism as well as for monitoring therapy in dogs with hyperadrenocorticism treated with Lysodren, Trilostane and Ketoconazole. Cosyntropin (Cortrosyn®), a synthetic ACTH gel, is the only drug currently available that has proven to be effective for stimulation testing in dogs. Recently prices have sky-rocketed for this already expensive drug and manufacturer issues have intermittently made the drug difficult to obtain. Due to price and demand, formulating pharmacies have recently been producing ACTH but its effectiveness has not been evaluated. The purpose of this study was to examine formulated ACTH from 4 different pharmacies to assess efficacy for ACTH stimulation testing compared to Cosyntropin.

5 mixed breed healthy dogs were used in the study. ACTH stimulation tests were performed on 5 different dates using Cosyntropin and 4 formulations in random order from 4 different pharmacies. The formulating pharmacies were (a) Pet Health Pharmacy, (b) Wedgewood Pharmacy, (c) Red Oak Drug and (d) Med For Vets. Cosyntropin was administered at 5 mcg/kg IV. The ACTH formulations were administered at 2.2 u/kg IM. Cortisol levels were obtained before administration and at 30, 60, 90 and 120 minutes. Serum cortisol levels from Cortrosyn stimulations were used as controls. Immunoreactive ACTH levels were evaluated for Cortrosyn and each of the formulated medications. Data were analyzed using a 2 way ANOVA for repeated measures.

Cortisol levels were similar to controls at 0, 30 and 60 minutes. Cortisol levels were lower than controls at 90 and 120 minutes in 2 of the ACTH formulations (a, d). Some of those samples were at baseline levels. Cortisol levels were higher at 120 minutes from one of the formulations (c). ACTH levels varied widely between the formulations (11, 52, 925 and 813 PG/ML).

This study shows that although all the ACTH compounds from the 4 pharmacies were effective at stimulating maximal cortisol production compared to cosyntropin the time to maximal response was varied at different time periods. ACTH activity was markedly different between manufacturers. If formulated ACTH is used, consider measuring multiple time points after administration with at least the 1 and 2 hour levels obtained. Efficacy of formulations from alternative pharmacies to those listed above is unknown without similar testing. This study did use the low dose of Cosyntropin which was shown to be effective in a study presented at last years conference resulting in a substantial cost savings. A separate study presented at this conference also showed that IM Cosyntropin administration had a similar cortisol stimulation effect compared to the standard IV route allowing greater ease of administration.

PLASMA CONCENTRATIONS OF ENROFLOXACIN IN CATS AFTER TRANSDERMAL ADMINISTRATION OF A PLO GEL FORMULATION

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Medications formulated in PLO (plurionic lecithin organogel) transdermal gel are being produced and marketed by formulating pharmacies as an alternative to oral forms for difficult to medicate cats. As availability and popularity have increased several drug types have been marketed without proven effectiveness when administered transdermally. Previous published studies of PLO formulated medications have shown highly variable and often minimal absorption. Currently only methimazole, fentanyl, dexamethasone, amitriptyline, buspirone and fluoxetine have been evaluated. Only methimazole and fentanyl have been shown to have consistent, adequate and reliable absorption and efficacy. This prospective study was performed to evaluate the serum levels of enrofloxacin from a formulated transdermal PLO. Four healthy cats were dosed with 0.1 ml of a 227 mg/ml PLO of enrofloxacin in the hairless area of the right inner pinna once daily. Serum levels were obtained at 0, 30, 60 and 120 minutes after either 1 or 3 doses with a 3 month washout between tests. Samples were evaluated for ciprofloxacin and enrofloxacin serum levels using a reverse-phase high-pressure liquid chromatography with fluorescence detection. The limit of quantification was 0.05 ug/ml.

No samples obtained at any time points had detectable serum levels of either ciprofloxacin or enrofloxacin.

This study shows that at least with enrofloxacin there is was significant transdermal absorption. Until appropriate studies are performed efficacy of any transdermal medications except fentanyl and methimazole should be questioned.

DIURETIC EFFICACY OF SPIRONOLACTONE WHEN USED IN CONJUNCTION WITH FUROSEMIDE IN HEALTHY GREYHOUNDS

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Spironolactone is an aldosterone-receptor blocker acting on the distal tubule of the kidney. Although commonly used as a diuretic in ascites from right sided heart failure, portal hypertension, and with pulmonary edema from left sided congestive heart failure, it's efficacy in dogs has been unproven. It has recently been expounded as an adjunct to standard treatment for congestive failure based on aldosterone's implication in the development of reactive interstitial fibrosis in experimental canine heart failure and from a report that life expectancy was prolonged in humans with heart failure when spironolactone was administered concurrently with conventional therapy. In a report from the 2004 ACVIM forum spironolactone failed to induce diuresis in healthy beagles. Most clinical cases of humans and dogs in congestive failure using spironolactone are also being treated with furosemide. Furosemide acts on the ascending limb of Henle which increases sodium excretion. One of the theories cited for the lack of efficacy in the previous study was a lack of concurrent furosemide administration. Furosemide increases delivery of sodium to the distal tubule which could allow spironolactone to exert a more significant effect. This study was designed to assess the diuretic effect of spironolactone when used in combination with furosemide in healthy dogs.

The study used 6 healthy greyhounds in a randomized crossover study with a 2 week washout. They were administered furosemide alone or furosemide + spironolactone. The doses were 2 mg/kg spironolactone PO BID and 3 mg/kg furosemide PO BID. Two 24 hr urine collections were obtained using a closed system in 5 dogs and free catch in one dog. Urine volume, PCV, body weight, urine electrolytes and serum creatinine and BUN were determined every 6 hours during the collection period.

There were no significant differences between groups in any of the measured parameters.

This study documents a lack of any diuretic effect of spironolactone when used in combination with furosemide. Dogs with heart failure have excessive stimulation of the renin-angiotensin-aldosterone pathway which could alter the efficacy of spironolactone. Further study is needed to assess the efficacy in dogs with congestive failure.

COMPARISON OF GLARGINE AND LENTE INSULIN IN CATS WITH DIABETES MELLITUS

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Glargine (Lantus®) is a genetically modified human recombinant insulin. The insulin is used in humans as a basal insulin which is relatively peakless with a sustained activity. There have been recent reports of its use in cats with diabetes mellitus. Recently the manufacturer Eli Lilly has announced it will discontinue production of recombinant human Lente insulin. This study was designed to compare the efficacy of glargine insulin at a once daily dose versus Lente insulin administered twice daily.

The study used 13 newly diagnosed or difficult to control diabetic cats randomized to either glargine (6 cats) or Lente (7 cats). All cats were fed Purina DM diet. Glargine was administered at an initial dose of 0.5 U/kg SQ SID and Lente insulin at 0.5 U/kg SQ BID. A 16 hr blood glucose curve at 2 hour intervals, fructosamine level, body condition score and body weight evaluated at 1, 2, 4, 8, and 12 weeks. Insulin levels were adjusted at these times based on the glucose curve and fructosamine level results.

Thirteen of 17 cats finished the study. One cat was expelled due to aggression and 3 cats died, one each from ketoacidosis, anesthetic complications and cancer. There was a statistically significant reduction in fructosamine levels and mean blood glucose curve values in all cats in both groups. Seven of 13 cats were considered adequately controlled, 4 of 13 had a complete remission and in 2 of 13 with difficult to control diabetes there was a marked reduction in insulin requirements. There was no significant difference in the measured parameters between the glargine or Lente groups.

This study shows that glargine is a viable option to Lente insulin for control of diabetes in cats. Glargine can also be used effectively as a once daily insulin. In combination with a high protein, low carbohydrate diet glargine can induce clinical remission of diabetes mellitus. In a separate study presented at this same conference glargine was compared to PZI and Lente insulin. All cats were also fed Purina DM. The cats treated with glargine had a lower mean glucose level and lower mean fructosamine level than the PZI and Lente treated cats. In addition the 8 cats treated with the glargine all went into remission from their diabetes within 4 months of starting treatment, a significantly higher percentage than either PZI or Lente.