Plasma cortisol response to ketoconazole administration in dogs with hyperadrenocorticism

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Summary: The effect of orally administered ketoconazole on plasma cortisol concentration in dogs with hyperadrenocorticism was evaluated. Every 30 minutes from 0800 hours through 1600 hours and again at 1800 hours, 2000 hours, and 0800 hours the following morning, 15 clinically normal dogs and 49 dogs with hyperadrenocorticism had plasma samples obtained and analyzed for cortisol concentration. The mean (± SD) plasma cortisol concentration for the initial 8-hour testing period was highest in 18 dogs with adrenocortical tumor (5.3 ± 1.6 µg/dl), lowest in 15 control dogs (1.3 ± 0.5 µg/dl), and intermediate in 31 dogs with pituitary-dependent hyperadrenocorticism (PDH; 3.4 ± 1.2 µg/dl). Results in each of the 2 groups of dogs with hyperadrenocorticism were significantly (P < 0.05) different from results in control dogs, but not from each other. The same cortisol secretory experiment was performed, using 8 dogs with hyperadrenocorticism (5 with PDH; 3 with adrenocortical tumor) before and after administration at 0800 hours of 15 mg of ketoconazole/kg of body weight. Significant (P < 0.05) decrease in the 8-hour mean plasma cortisol concentration (0.9 ± 0.2 µg/dl) was observed, with return to baseline plasma cortisol concentration 24 hours later.

Twenty dogs with hyperadrenocorticism (11 with PDH, 9 with adrenocortical tumor) were treated with ketoconazole at a dosage of 15 mg/kg given every 12 hours for a half month to 12 months. The disease in 2 dogs with PDH failed to respond to treatment, but 18 dogs had complete resolution of clinical signs of hyperadrenocorticism and significant (P < 0.05) reduction in plasma cortisol responsiveness to exogenous adrenocorticotropic (ACTH). The healthy control dogs had a mean baseline plasma cortisol concentration of 1.4 ± 0.4 µg/dl and a post-ACTH cortisol concentration of 70.6 ± 31.1 µg/dl. Before ketoconazole administration, all 11 dogs with PDH had a mean baseline plasma cortisol concentration of 4.4 ± 1.9 µg/dl and a post-ACTH cortisol concentration of 33.6 ± 17.6 µg/dl. The 9 dogs with adrenocortical tumor had a mean baseline plasma cortisol concentration of 4.4 ± 1.3 µg/dl and post-ACTH cortisol concentration of 28.1 ± 14.1 µg/dl. After 5 days of ketoconazole administration, the post-ACTH plasma cortisol concentration for dogs with PDH or adrenocortical tumor was 4.3 ± 5.4 µg/dl and 6.0 ± 3.3 µg/dl, respectively. Similar responses were observed after 60, 180, and 360 days of ketoconazole treatment.

Hyperadrenocorticism is a common endocrine disorder in dogs.1-2 Excess secretion of pituitary adrenocorticotropic (ACTH), with resultant bilateral adrenocortical hyperplasia (pituitary-dependent hyperadrenocorticism; PDH), is responsible for hyperadrenocorticism that develops in 80 to 90% of affected dogs. The disease is usually the result of ACTH secretion from an adenoma of the pars distalis or pars intermedia, and is less commonly caused by pituitary carcinoma or hyperplasia.1 The remainder of dogs (10 to 20%) with hyperadrenocorticism have functional adrenocortical adenoma or carcinoma.2 Dogs with PDH are usually treated with the adrenocorticolytic agent mitotane and less commonly by use of surgery or irradiation.3-6 Dogs with adrenocortical tumor are usually treated surgically and, less commonly, with mitotane.6

Ketoconazole, an imidazole derivative, is an antifungal agent that is active after oral administration. In addition to its antifungal activity, ketoconazole has been shown to interfere with gonadal and adrenal steroid synthesis through inhibition of cytochrome P-450-dependent enzymes. Similar endocrinologic effects have been observed in clinically normal dogs.1, 2 The study reported here was undertaken to assess the effect of ketoconazole administration on plasma cortisol concentration in dogs with hyperadrenocorticism.

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dogs with PDH and in those with hyperadrenocorticism caused by a functional adrenocortical tumor.

Materials and Methods

Clinically normal dogs—Fifteen privately owned pet dogs (7 sexually intact males; 8 ovariectomized females) were used as controls. Dogs ranged in age from 1 to 10 years, with mean (± SD) of 5.3 (± 1.8) years. Body weight was between 8.5 and 42.1 kg, with a mean of 22.2 (± 10.8) kg. Dogs were not being given any medication. Each dog was healthy based on review of history and physical examination findings. Control dogs also had normal results of CS, serum biochemical analysis and urinalysis.

Dogs with hyperadrenocorticism—Sixty privately owned pet dogs (39 females; 21 males) with hyperadrenocorticism were studied. Dogs ranged in age from 4 to 16 years, with mean of 10.2 (± 2.1) years. Sixteen breeds were represented. The suspicion of hyperadrenocorticism was based on clinical signs of disease (eg, polydipsia, polyuria, polyphagia, alopecia, thin skin, and muscular weakness) and laboratory findings (eg, lymphopenia, eosinopenia, high serum alkaline phosphatase activity and cholesterol concentration, and dilute urine specific gravity). The diagnosis of hyperadrenocorticism was confirmed in all dogs by detection of an abnormal and exaggerated increase in plasma cortisol concentration 1 hour after intravenous administration of 0.25 mg of synthetic ACTH13/iv/dog and/or inadequate suppression of the plasma cortisol concentration 8 hours after IV administration of dexamethasone sodium phosphate (0.01 mg/kg of body weight). A tentative diagnosis of functioning adrenocortical tumor was assigned to 22 dogs in which endogenous ACTH concentration was not detectable (< 10 pg/ml) in a randomly obtained morning (0800 to 1000 hours) plasma sample.14 Unilateral or bilateral adrenocortical tumors (adenoma or carcinoma) were subsequently confirmed by results of laparotomy or necropsy in each of these 22 dogs.

Of the 60 dogs with hyperadrenocorticism, PDH was tentatively diagnosed in 38 of them. This classification was based on finding morning (between 0800 and 1000 hours) endogenous ACTH concentration > 40 pg/ml in a randomly obtained sample from each of these dogs and/or suppression of plasma cortisol concentration 8 hours after IV administration of dexamethasone at a dose of 0.1 mg/kg.13 Of these 38 dogs, 16 died and had pituitary tumor, as well as bilateral adrenocortical hyperplasia, identified at necropsy. The tumor was tentatively described as pars distalis tumor in 8 dogs and pars intermedia tumor in 4 dogs. The origin of 4 pituitary tumors could not be identified. Nine dogs with adrenocortical tumors and 11 dogs with PDH were given ketoconazole prior to any other form of treatment.

Cortisol secretion experiment—Twenty-four hours before testing began, 64 dogs (15 clinically normal; 49 with hyperadrenocorticism) were hospitalized, and an indwelling catheter was inserted into one external jugular vein. The dogs with hyperadrenocorticism (31 with PDH; 18 with adrenocortical tumor) had this diagnosis confirmed at our facility, had not been treated, and had not undergone any endocrine studies in the preceding 30 days. Catheterization was completed in each dog without use of anesthesia or sedation. The day after the catheter was placed, plasma cortisol concentration was assessed every 30 minutes from 0800 through 1600 hours—and at 1800, 2000, and 0800 hours the following morning. All dogs were housed in individual runs or cages, and blood samples were obtained via IV catheter. Strict control of light and dark was not attempted. All dogs were fed a commercial dog food diet (to which they were accustomed) at 0800 hours and again at 1800 hours before and during the sample collection period. Water was always available. Four dogs with hyperadrenocorticism also had endogenous ACTH concentration monitored during the sample collection period, in addition to assessment of plasma cortisol concentration.

Cortisol secretion experiment in dogs given ketoconazole—Prior to ketoconazole administration, 8 dogs (5 with PDH; 3 with adrenocortical tumor) had plasma cortisol concentration determined every 30 minutes from 0800 to 1600 hours, and at 1800, 2000, and 0800 hours the next morning, as previously described. This same protocol was repeated the morning after initial oral administration of 15 mg of ketoconazole/kg, immediately after the 0800-hour blood sample was collected. None of these dogs had been treated previously for hyperadrenocorticism.

Adrenocorticotropin stimulation testing in dogs given long-term ketoconazole—An ACTH stimulation test was performed on 15 privately owned healthy dogs and on 60 dogs with spontaneous hyperadrenocorticism. The long-term effect of ketoconazole administration was assessed in 20 of the 60 privately owned dogs with hyperadrenocorticism. Dogs ranged in age from 6 to 16 years, with mean of 10.1 (± 1.8) years. Twelve were female. These 20 dogs (11 with PDH; 9 with adrenocortical tumor) were given 30 mg of ketoconazole/kg, orally, divided into 2 equal doses, for 0.5 to 12 months. Other medications were not administered. An ACTH stimulation test was performed prior to initiation of ketoconazole administration and again on treat-

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The original study identified 11 dogs to any one group, but due to any inconsistency-four dogs were housed in one cage, three dogs were housed in another cage, one dog was inserted with a catheter, one dog was removed with a catheter, and one dog was removed due to a clinical condition. All dogs were housed in a room that had been previously monitored in the clinical environment. The room was maintained at a temperature of 21°C and a relative humidity of 50%. All dogs were fed a commercial diet specifically formulated for dogs. The study design included a 2-month treatment period, during which they received either 4 or 12 months of treatment. All dogs were monitored for any apparent side effects to the treatment regimen.

Hormone assay—Blood samples obtained for plasma cortisol were immediately centrifuged, and the plasma was frozen. Plasma cortisol concentration was determined by inhibition of the ACTH immunoreactive hormone. The assay used antisera raised in rabbits to cortisol-3-0-carboxymethylxime-bovine serum albumin immunogen and cortisol-3-0-carboxymethylxime-horse radish peroxidase as the label. The assay was specific for cortisol. Cross-reactivity to other corticosteroids was: prednisone, 6.3%; prednisolone, 9.9%; 11-deoxycortisol, 6%; cortisone, 5%; and corticosterone, 0.7%. For all other steroids, including dexamethasone, cross-reactivity was lower. Cortisol standards were prepared in ethanol to give a standard curve range of 0.1 to 250 pg/well. The intraassay coefficient of variation was 1.9%. The interassay precision determinations gave coefficients of variation of 8.8% for low (0.9 µg/dl, n = 45), 7.3% for medium (18.6 µg/dl, n = 41), and 8% for high (41.2 µg/dl, n = 40) concentrations of cortisol in 3 pooled serum samples. The interassay coefficients of variation were 12.4, 10.5, and 6.8% for the same 3 pools of serum. The sensitivity of the system was 0.25 pg/well or 0.05 µg of cortisol/dl in canine plasma. Recovery was determined by assaying several samples to which various known amounts of cortisol had been added: average recovered was 98.8%, with range of 94 to 104%. Blood samples for endogenous ACTH assays were handled as described. Endogenous ACTH concentration was determined by radioimmunoassay, with a reference range of 20 to 100 pg/ml established for normal dogs.

Statistical analysis—All results are reported as mean ± SD, unless otherwise indicated. Data were analyzed by use of repeated-measures analyses of variance. Differences between group means were evaluated, using the Student-Newman-Keuls test. Values of P < 0.05 were considered significant.

Results

Cortisol secretion experiment—The 8-hour mean plasma cortisol concentration from samples obtained every 30 minutes (beginning at 0800 hours and ending at 1600 hours) was significantly (P < 0.05) different when each group of dogs with hyperadrenocorticism (PDI and adrenocortical tumor) was compared with the control group. However, values in the 2 groups with hyperadrenocorticism were not significantly different from each other (Fig 1). The 8-hour mean plasma cortisol concentration for the entire period was highest in the 18 dogs with functioning adrenocortical tumor (5.3 ± 1.6 µg/dl), lowest in the 15 clinically normal dogs (1.3 ± 0.3 µg/dl), and intermediate in the 31 dogs with PDI (3.4 ± 1.2 µg/dl).

![Figure 1: Mean (± SD) plasma cortisol concentrations every 30 minutes from 0800 through 1600 hours in 15 healthy dogs (●●●●), 31 dogs with pituitary-dependent hyperadrenocorticism (PDI) (●●●●), and 18 dogs with adrenocortical tumors (○○○○). At each time point, values in the control dogs were significantly (P < 0.05) less than values in both groups of dogs with hyperadrenocorticism.](image)

Plasma was obtained for endogenous ACTH determination from 4 dogs (2 with adrenocortical tumors, 2 with PDI) every 30 minutes beginning at 0800 hours and ending at 1600 hours. The endogenous ACTH concentration from each of the dogs with adrenocortical tumors was below the detection limit of the assay (eg, <10 pg/ml). The 2 dogs with PDI had endogenous ACTH concentrations that fluctuated between 62 to 145 pg/ml and 102 to 188 pg/ml.

Cortisol secretion after the initial dose of ketoconazole—The administration of ketoconazole in the initial, orally administered dose (15 mg/kg at
0800 hours) significantly \((P < 0.05)\) decreased the mean 8-hour serial cortisol concentration from \(3.9 \pm 0.5 \mu g/dl\) to \(0.9 \pm 0.2 \mu g/dl\) in the 3 dogs with adrenocortical tumor and in the 5 dogs with PHM. Differences were not seen by comparing response to ketoconazole in dogs with adrenocortical tumors vs those with PHM. The 8-hour mean cortisol concentration in the 15 healthy dogs \((1.3 \pm 0.5 \mu g/dl)\) was not significantly different from the 8-hour mean post-ketoconazole cortisol concentration in the dogs with hyperadrenocorticism \((P < 0.05)\). Mean plasma cortisol concentration progressively returned toward pretreatment values at 1800 hours \((2.6 \pm 1.3 \mu g/dl)\) vs \(3.2 \pm 1.2 \mu g/dl\) \((P < 0.05)\), 2000 hours \((3.4 \pm 2.9 \mu g/dl)\) vs \(3.6 \pm 1.3 \mu g/dl\) \((P < 0.05)\), and at 0800 hours the morning after ketoconazole was administered \((4.2 \pm 1.1 \mu g/dl)\) vs \(3.9 \pm 1.1 \mu g/dl\) \((P < 0.05)\). Prior to treatment, there was no significant difference between the 0800- to 1600-hour serial cortisol concentrations in the 31 dogs \((2.3 \pm 1.2 \mu g/dl)\) of the cortisol secretion experiment, compared with the 5 dogs \((2.2 \pm 1.4 \mu g/dl)\) of the ketoconazole experiment. There was also no significant difference between the 0800- to 1600-hour serial cortisol concentrations in the 18 dogs \((2.2 \pm 1.2 \mu g/dl)\) of the cortisol secretion experiment and the 3 dogs with adrenocortical tumor that subsequently were given ketoconazole.

![Diagram](https://via.placeholder.com/150)

**Figure 2**—Mean \((\pm SD)\) plasma cortisol concentrations every 30 minutes from 0800 through 1600 hours and again at 1800, 2000, and 0800 hours \((P < 0.05)\) in 5 dogs with hyperadrenocorticism \((P < 0.05)\) which were administered ketoconazole \((2.5 \mu g/kg)\) immediately after obtaining the 0800-hour blood sample \((O---O)\). Plasma cortisol concentrations in 15 healthy, untreated control dogs are included \((\bullet---\bullet)\). Ketoconazole caused significant \((P < 0.05)\) reductions in plasma cortisol concentration from 0830 through 1600 hours.

Adrenocorticotropic stimulation testing after long-term ketoconazole administration—The mean baseline cortisol concentration was \(1.4 \pm 0.4 \mu g/dl\) in 15 healthy control dogs. After ACTH administration, the mean cortisol concentration in control dogs was \(10.6 \pm 3.1 \mu g/dl\) A post-ACTH cortisol concentration \(>20.0 \mu g/dl\) \((>3 \times SD)\) above the reference mean was considered an abnormal response, suggestive of hyperadrenocorticism. Mean baseline plasma cortisol concentration in the 60 dogs with hyperadrenocorticism was \(4.0 \pm 3.3 \mu g/dl\) and the mean post-ACTH plasma cortisol concentration was \(25.2 \pm 8.7 \mu g/dl\).

The mean baseline plasma cortisol concentration in the 38 dogs with PHM was \(3.3 \pm 3.7 \mu g/dl\) and, after ACTH stimulation, was \(24.2 \pm 8.0 \mu g/dl\). Eleven dogs with PHM were treated with ketoconazole. Before ketoconazole treatment, plasma cortisol concentrations before and after ACTH administration were \(4.4 \pm 1.9 \mu g/dl\) and \(33.6 \pm 17.6 \mu g/dl\), respectively. The mean baseline and post-ACTH plasma cortisol concentrations in the dogs with PHM treated with and responding to ketoconazole were significantly \((P < 0.01)\) lower on treatment days 5, 60, 180, and 360, compared with pretreatment values. On ketoconazole treatment day 5, the mean baseline plasma cortisol concentration in 9 dogs with PHM was \(1.9 \pm 2.0 \mu g/dl\) and the post-ACTH value was \(4.0 \pm 5.4 \mu g/dl\). On treatment day 60 in these 9 dogs, the mean baseline plasma cortisol concentration was \(1.8 \pm 1.2 \mu g/dl\) and the post-ACTH value was \(6.4 \pm 4.8 \mu g/dl\). On treatment days 180 and 360, the mean baseline plasma cortisol concentrations were \(2.4 \pm 1.0 \mu g/dl\) and \(4.9 \pm 0.4 \mu g/dl\), respectively; the post-ACTH values were \(5.8 \pm 2.6 \mu g/dl\) and \(6.0 \pm 3.2 \mu g/dl\), respectively \((P < 0.01)\).

The post-ACTH plasma cortisol concentration was significantly lower \((P < 0.01)\) on treatment days 5, 60, 180, and 360, compared with the response to ACTH in the 15 control dogs. Of the 11 dogs with PHM given ketoconazole, treatment was discontinued in 2 because of failure to respond; 3 were euthanatized between the 180th and 360th days of treatment (see later discussion); and 5 were subsequently treated with an alternative medication, 3 after 60 days and 2 after 180 days of ketoconazole administration.

The mean baseline plasma cortisol concentration in the 22 dogs with adrenocortical tumor was \(4.2 \pm 1.4 \mu g/dl\) and the post-ACTH value was \(26.0 \pm 6.4 \mu g/dl\). The mean pre-ketoconazole administration baseline and post-ACTH plasma cortisol concentrations in the 9 dogs with adrenocortical tumor were \(4.4 \pm 1.3 \mu g/dl\) and \(28.1 \pm 14.1 \mu g/dl\), respectively. The mean baseline and post-ACTH plasma cortisol concentrations in these 9 dogs after ketoconazole administration were significantly \((P < 0.01)\) lower on treatment days 5, 60, 180, and 360, compared with pretreatment values. On ketoconazole treatment day 5, the mean baseline plasma cortisol concentration in these 9 dogs was \(1.6 \pm 1.2 \mu g/dl\) and the post-ACTH value was \(6.1 \pm 3.3 \mu g/dl\). By treatment day 60, ketoconazole administration was continued in 7 of the 9 dogs with adrenocortical tumor, and 2 had undergone surgical extirpation of the tumors. In the 7 dogs continuing ketoconazole treatment, the mean
Endogenous ACTH concentration during ketoconazole treatment—Three dogs with pDH had endogenous ACTH concentration determined over a 4- to 12-month ketoconazole treatment period, before treatment, endogenous ACTH concentration was 67, 47, and 85 pg/ml, with mean of 66.3 (± 19) pg/ml. During treatment, endogenous ACTH concentration was 83, 17, and 56 pg/ml, respectively, with mean of 52 (± 33) pg/ml. At the time of the second endogenous ACTH assessment in each dog, remission of clinical signs of hyperadrenocorticism and subnormal plasma cortisol response to exogenous ACTH had been observed. Endogenous ACTH determination was performed serially on 1 dog with adrenocortical tumor. Change in ACTH concentration (<10 pg/ml) was not seen after 9 weeks of ketocanazole administration, despite clinical improvement and subnormal plasma cortisol response to exogenous ACTH.

Clinical evaluation—All 9 dogs with adrenocortical tumor and 9 of 11 dogs with pDH responded to ketoconazole. This response not only included suppression of plasma cortisol concentration, but also marked and long-term improvement in clinical condition. Remission of polydipsia, polyuria, polyphagia, and other signs of hyperadrenocorticism were observed in these 18 dogs. One of these 18 dogs had gastrointestinal side effects (anorexia, vomiting) that necessitated temporary discontinuation of treatment. Two dogs failed to respond to the drug, as previously mentioned.

During or after the study, 6 dogs were euthanized because of problems thought to be unrelated to ketoconazole administration. One of 2 dogs with pDH that was euthanized had heart failure, and the other had renal failure. These problems had been identified prior to initiation of ketoconazole treatment. The 4 dogs with adrenocortical tumors that were euthanized each had tumor metastasis that caused cachexia, weakness, and related signs of disease. Necropsy findings confirmed the antemortem diagnosis of pDH in 2 dogs. Both dogs had bilateral adrenocortical hyperplasia. One had solitary pars distalis adenoma, and the other had solitary pars intermedia adenoma. The other 2 dogs had adrenocortical carcinoma confirmed at necropsy. The 5 remaining dogs with adrenocortical tumors are alive after surgical and histologic confirmation of the diagnosis. The remaining 9 dogs with pDH are alive and well, and are being treated with ketoconazole (n = 2) or metoatep (n = 7).

Discussion

Loss of normal circadian rhythmicity of the hypothalamic–pituitary–adrenal axis is one of the hallmark signs of hyperadrenocorticism in people.18,19 Previous studies20,21 indicate that clinically normal dogs do not appear to have circadian rhythm in plasma proopiomelanocortin peptide or cortisol.

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Figure 3—Mean (±SE) baseline and post-ACTH plasma cortisol concentrations in dogs with hyperadrenocorticism before and at 5, 60, 180 (6 dogs), and 360 (2 dogs) days during ketoconazole administration. After initiation of ketoconazole treatment (15 mg/kg, q 12 h), all baseline (pre) and post-ACTH (post) plasma cortisol concentrations were significantly (P < 0.05) lower than the pretreatment values. Test results from 15 control dogs (N = 10) are included (••••••).

A—Values in dogs with pDH. Numbers at each time point indicate number of dogs on test at that time; Rx = ketoconazole treatment

B—Values in dogs with adrenocortical tumor. Numbers at each time point indicate number of dogs on test at that time; Rx = ketoconazole treatment.
concentrations, although secretion is episodic, as it is in people.22,23 Dogs with PDM appear to have normal frequency of secretory episodes, but of greater amplitude, resulting in high mean daily plasma cortisol concentration. This has been documented in some human patients with hyperadrenocorticism.24 We have documented in this report that dogs with spontaneous PDM and those with cortisol-secreting adrenocortical tumors have significantly higher mean daily plasma cortisol concentration than do clinically normal dogs. The lack of circadian rhythm in clinically normal dogs allowed the use of pet dogs, those that were healthy as well as those with hyperadrenocorticism, because strict control of light and dark periods was not needed.

Ketoconazole effectively blocks cortisol synthesis in dogs with PDM as well as in those with adrenocortical tumor. Similar results with ketoconazole have been reported in the management of hyperadrenocorticism in people.25-30 Ketoconazole (15 mg/kg) given to the dogs of our study resulted in a rapid reduction in baseline plasma cortisol concentration. That dose, administered twice daily, resulted in a significant reduction in plasma cortisol response to exogenous ACTH. The inhibition of cortisol synthesis in 18 of the dogs with hyperadrenocorticism was sustained throughout the treatment period, as evidenced by pre- and post-cortisol responses to exogenous ACTH. Such responses were below control values at treatment days 5, 60, 120, 180, and 360, and the physical characteristics and clinical signs of hyperadrenocorticism were alleviated during the same period.

Ketoconazole was an effective therapeutic drug in dogs with PDM and adrenocortical tumor. Therefore, the pathway of cortisol synthesis was inhibited by ketoconazole as an enzyme blocker, regardless of the cause of excess cortisol secretion. Little or no reduction in plasma cortisol concentration was observed after administration of ketoconazole at a dosage of 5 mg/kg every 12 hours (data not shown).

As can be seen in Figure 2, the reduction in plasma cortisol concentration was rapid after initial administration of ketoconazole to 8 dogs with hyperadrenocorticism. Within 30 minutes, significant reduction in cortisol concentration was observed. The half-life of cortisol in the circulation has been estimated to be 60 to 90 minutes,31 thus, the rapid action of ketoconazole was striking. The plasma cortisol concentration decreased quickly, and the effects of a single dose of ketoconazole lasted as long as 8 to 12 hours, but <24 hours.

Ketoconazole was not only an effective inhibitor of cortisol synthesis in the short term, but over a period of months as well. Sixteen dogs with hyperadrenocorticism were well controlled for at least 60 days. Four of these dogs were treated for at least 12 months without problems. Ketoconazole administration was discontinued because of availability of alternative treatment (surgery and/or mitotane administration) that was less expensive or more efficacious.

Two dogs failed to respond to ketoconazole. Ketoconazole has been shown to have unpredictable bioavailability when administered orally to dogs and people.32 Failure to respond, therefore, could have been the result of poor intestinal absorption of ketoconazole. Assessment of therapeutic concentration of the drug in serum or plasma may be necessary to help identify individuals who may not be absorbing ketoconazole from the intestinal tract. One dog developed gastrointestinal side effects that prompted the owner to discontinue medication. Ketoconazole overdosing could result in hypercortisolism, with clinical signs consistent with this disease.33 Such signs include vomiting, diarrhea, anorexia, weakness, and depression, which were observed in the aforementioned dog. The dog rapidly responded to discontinuation of ketoconazole administration and prednisolone treatment after that, which ketoconazole was successfully reinstituted at a slightly lower dose.

A compensatory increase in endogenous ACTH concentration was seen when ketoconazole was administered in high doses to people with normal function of the hypothalamic-pituitary-adrenal axis.34 However, this compensatory increase in ACTH concentration has not been observed in people with either Cushing's disease or Cushing's syndrome, despite marked reductions in their plasma and urinary cortisol concentrations.25,26,34 This would appear to be true in dogs as well, because ketoconazole had little effect on endogenous ACTH concentration in 4 affected dogs treated for 2 to 12 months. In contrast, after treatment with the adrenocorticolytic agent mitotane, a twofold increase in endogenous ACTH concentration has been documented in dogs with PDM.16

The mechanism(s) responsible for the lack of a compensatory increase in ACTH concentration are not known. It has been shown that the ACTH response to corticotropin-releasing factor during the administration of ketoconazole was unchanged, compared with the pretreatment response in human patients with Cushing's disease.25 This finding provides evidence against the concept that ketoconazole has an inhibitory effect at the pituitary gland level and that long-term ketoconazole treatment may in some way modify the hypothalamic-pituitary-adrenal axis in patients with Cushing's disease.35 However, it has been reported that ketoconazole inhibits corticotropin releasing factor-stimulated ACTH biosynthesis and release from rat anterior pituitary cells in vitro, through inhibition of the catalytic component of adenylate cyclase, resulting in decreased cyclic AMP generation.36,37 The clinical importance of this type of inhibition of

ACTH release in patients with hyperadrenocorticism is unknown.

In conclusion, the imidazole derivative ketaconazole was effective in decreasing plasma cortisol concentration in dogs with hyperadrenocorticism. The drug was equally effective in dogs with PDH and in dogs with hyperadrenocorticism attributable to adrenocortical adenoma or carcinoma. The effect of a single ketaconazole dose was observed within 30 minutes of administration and lasted <24 hours. Twice-daily treatment was successful in resolving clinical signs of hyperadrenocorticism in 18 of 20 dogs for at least 60 days and in 4 dogs for as long as 12 months. Two dogs failed to respond to ketaconazole, and 1 dog had evidence of hypocortisolism.

Our recommendations are to treat dogs with hyperadrenocorticism, using ketaconazole at a dosage of 5 mg/kg given every 12 hours for 7 days, merely to evaluate dogs for side effects such as acute hepatitis or gastritis. Although the authors' knowledge, such has not yet been reported in dogs, ketaconazole can cause hepaticopathy in people. This may result in anorexia, lethargy, jaundice, and abnormal liver enzyme activities. If no side effects are observed, the dosage should be increased to 10 mg/kg (q 12 h) for 14 days, and an ACTH stimulation test should be performed at that time. If no normal or exaggerated response to exogenous ACTH is observed, increase the ketaconazole dosage to 15 mg/kg (q 12 h) and continue to monitor the dog (as previously described) every 14 to 60 days.

As time, ketaconazole treatment is principally used before surgery in dogs with adrenocortical tumor or as the only mode of treatment, because such tumors are often resistant to mitotane; in dogs that do not tolerate mitotane; and in dogs in which ketaconazole treatment is used as a diagnostic aid. The authors are not aware of any chronic effects of ketaconazole on nonsteroid-producing body systems, as assessed by results of routine laboratory tests. In conclusion, ketaconazole is effective for decreasing plasma cortisol concentrations in most dogs with hyperadrenocorticism.

References

Effects of flunixin and flunixin plus prednisone on the gastrointestinal tract of dogs

Flunixin meglumine has been reported to induce gastrointestinal lesions in dogs when administered at therapeutic dosages. We administered flunixin meglumine to dogs daily for 10 days to assess the effect of this drug on the gastrointestinal tract. We also evaluated the possibility of corticosteroid potentiation of gastrointestinal toxicity by concurrent administration of prednisone to 1 group of dogs. Dogs were monitored for gastrointestinal toxicity by means of serial endoscopic evaluation, measurement of fecal occult blood, PCV, and total solid concentration, and by physical examination. There were 3 treatment groups of 5 dogs each. Group-1 dogs were given 2.2 mg of flunixin meglumine/kg of body weight daily, in 2 divided doses IM; group-2 dogs were given 4.4 mg of flunixin meglumine/kg daily, in 2 divided doses IM; and group-3 dogs were given 2.2 mg of flunixin meglumine/kg daily, in 2 divided doses IM, plus 1.1 mg of prednisone/kg orally, in 2 divided doses. A fourth group of 5 dogs served as a control group.

Endoscopically visible gastric mucosal lesions developed in all treated dogs within 4 days of initiation of treatment. Lesions first developed in the gastric pylorus and antrum, and lesions at these sites were more severe than those observed elsewhere. Dogs treated with flunixin meglumine plus prednisone developed the earliest and most severe lesions; lesion scores in group-2 dogs were higher than those in group-1 dogs. All dogs treated had occult blood in their feces by day 5, and its presence appeared to correlate more closely with endoscopic findings than did physical examination findings or changes in values for PCV or total solids.

Deep ulcers were observed in the pylorus of most treated dogs examined at necropsy on day 10. Shallow ulcers and erosions were in the small intestine of group-2 and -3 dogs. Capillary microthrombi, associated with lesions of coagulative necrosis of superficial epithelium, were found in the colonic and small intestinal mucosa of several dogs in groups 2 and 3, and were suggestive of vascular injury.

From results of this study, it was concluded that flunixin meglumine, administered at therapeutic doses, induced early gastric mucosal injury in dogs and that concurrent administration of prednisone may have exacerbated the gastrointestinal injury induced by flunixin alone.—Steven W. Dow, Rodney A. W. Rosychuk, Alexander E. McChesney, et al, Am J Vet Res, 51 (July 1990).