Trilostane Therapy for Treatment of Spontaneous Hyperadrenocorticism in Cats: 15 Cases (2004–2012)

A.M. Mellett Keith, D. Bruyette, and S. Stanley

Background: Medical treatment with trilostane improves clinical signs, causes unclear insulin requirement changes, and variable survival times in cats.

Objectives/Hypothesis: To characterize the long-term efficacy of trilostane in treating cats with hyperadrenocorticism (HAC).

Animals: Fifteen client-owned cats with spontaneous HAC.

Methods: Multicenter descriptive retrospective study with a search performed on all medical records for cats diagnosed with spontaneous HAC.

Results: Clinical signs (13 of 15 cats) and ACTH stimulation testing results (13 of 15) improved with trilostane therapy. Diabetes mellitus was reported in 9/15 cases. Insulin requirements decreased by 36% within 2 months in 6/9 diabetic cats. Median survival time was 617 days for all cats (range 80–1,278 days). Complications included weight loss, urinary tract infections, chronic kidney disease, seizures, and recurrent pancreatitis. Hypocortisolemia was documented in 1 case. Cause of death occurred as a result of nonadrenal or nondiabetic illnesses (renal failure, seizures [caused by hypoglycemia or unknown]), or lymphoma.

Conclusions and Clinical Importance: Trilostane ameliorates clinical signs of HAC in cats, is tolerated well in the long term, and can lead to improved regulation of diabetes.

Key words: Cushing's syndrome; Endocrinopathy; Feline; Steroid synthesis inhibitor.

Data regarding spontaneous hyperadrenocorticism (HAC) in cats are available for approximately 90 cats since 1975. Similar to dogs, 85% of affected cats have pituitary-dependent hyperadrenocorticism (PDH), with the remainder having adrenal tumors.[1] Eighty percent of cats have concurrent diabetes mellitus (DM), but not all cats with HAC and DM have insulin resistance. Administration of medications such as mitotane, ketoconazole, and metyrapone has resulted in a poor long-term prognosis. Adrenalectomy has important postsurgical complications and other treatments, such as transsphenoidal hypophysectomy, laparoscopic adrenalectomy, and irradiation of pituitary tumors, are not readily available.[2–8] Trilostane, a competitive 3-beta hydroxysteroid dehydrogenase inhibitor, successfully controls clinical signs in dogs with HAC and resulted in successful treatment of 5 HAC cats.[a,9] There was improvement in clinical signs and endocrine testing results, but insufficient information to conclude if insulin requirements were reduced in the 3 diabetic cats. Poor long-term survival (death within 16, 140 days) occurred in 2 of 5 cats, with the other 3 surviving at least 6–20 months after starting trilostane therapy.

Trilostane is hypothesized to be a well-tolerated treatment option for long-term medical management of HAC in cats and as cortisol is a powerful insulin antagonist, successful treatment should improve glycemic control.

Abbreviations:

AG	adrenal gland
AP	acute pancreatitis
DM	diabetes mellitus
fPLI	feline pancreatic lipase immunoreactivity
GFR	glomerular filtration rate
HAC	hyperadrenocorticism
IGF-1	insulin-like growth factor 1
LDDST	low-dose dexamethasone suppression test
PDH	pituitary-dependent hyperadrenocorticism
PU/PD	polyuria/polydipsia
RF	renal failure
UTI	urinary tract infection

Materials and Methods

Medical records of 15 cats that received trilostane for treatment of HAC were reviewed. Information retrieved included signalment, history, physical examination findings, comorbidities, clinical laboratory results, endocrine function testing, diagnostic imaging findings, treatment protocols, and treatment response. Records were identified by performing computerized searches of medical databases for cats diagnosed with spontaneous HAC through multiple institutions. Diagnostic/inclusion criteria included a complete medical record, appropriate history and clinical signs, ultrasound imaging of the adrenal glands (AGs), and endocrine test results consistent with HAC with at least 1 follow-up ACTH stimulation test. Exclusion criteria included an incomplete medical record, no follow-up testing results, or trilostane treatment received for less than 60 days.

From the Section of Internal Medicine, School of Veterinary Medicine, University of Pennsylvania, Philadelphia, PA (Mellett Keith, Stanley); and the Section of Internal Medicine, VCA West Los Angeles Animal Hospital, Los Angeles, CA (Bruyette); and Dr Stanley is presently affiliated with the Fifth Avenue Veterinary Specialists, New York, NY.

Corresponding author: A.M. Mellett Keith, DVM, Section of Internal Medicine, Mission Veterinary Specialists, 8202 North Loop 1604 W #113 San Antonio, TX 78249; e-mail: drkeith@misisonvetspecialists.com.

Results

Signalment and Clinical Findings

There were 14 domestic shorthairs and 1 Bengal cat. Eight were spayed females and 7 were castrated males. Median age at diagnosis was 12.3 years (range 2.8–16.4). Body weight was 4.5 kg (median, range 2.9–7.8).

Dermatologic disease (dermal atrophy and skin wounds in 6, dermal atrophy in 4, and a pendulous abdomen in 1) in conjunction with lethargy and poorly regulated DM encompassed the presenting complaints (Table 1). Blood pressure monitoring was not consistently performed; in the 10/15 cases with a reported ultrasonic Doppler measurement, there was no evidence of hypertension. Fundic examination results were not recorded.

Clinicopathologic Data

Common abnormalities included hypercholesterolemia in 9/15, hyperglycemia in 8/15, and liver enzyme activity increases in 6/15. An increased serum BUN concentration with a normal serum creatinine concentration was found in 7/15. Proteinuria was detected in 5/10, glucosuria in 6/10 with negative ketonuria, and mild-to-moderate urine concentrating ability in all (range 1.014–1.043) urinalyses (10, representing 10 cats). Urine culture was negative in 6/7 cats and positive in 1. Feline pancreatic lipase immunoreactivity (fPLI) testing was increased in all 3 animals tested. Acute pancreatitis was suspected in 2/15 cases based on consistent clinical signs, abdominal ultrasound findings, an fPLI, or both.

Diagnostic Imaging

Thoracic radiographs including the cranial abdomen were performed in 12/15 cases at the time of diagnosis as part of a diagnostic workup for a poorly regulated diabetic, to assess the cardiovascular status, or both in cats with a heart murmur. Abnormalities included hepatomegaly in 7/12, cardiomegaly in 4/12, a mild bronchial pulmonary pattern in 1/12, and pleural effusion in 1/12.

Abdominal ultrasonography revealed bilateral adrenomegaly in 12/15 cases. Of the remaining 3, one had an enlarged left AG with a normal-sized right AG. Follow-up imaging revealed bilateral adrenomegaly. One case had borderline left adrenomegaly (left AG measured 5.4 mm, right measured 4 mm, normal width considered up to 5.3 mm) with a normal-sized contralateral AG, and the other case had a unilateral left adrenal mass with an atrophied right AG.[10]

Endocrine Testing

The most common diagnostic test for HAC (13 of 15 cats) was a low-dose dexamethasone suppression test (LDDST), performed by administering 0.1 mg/kg dexamethasone IV, with cortisol samples assayed at baseline, 4, and 8 hours postdexamethasone administration (Table 2). Higher doses of dexamethasone (0.1 mg/kg) are more reliably suppressive in cats with normal adrenal function, as lower doses (0.01 mg/kg) have the potential for false-positive diagnosis in cases

Table 1. Clinical findings at the time of diagnosis in 15 cats with HAC.

	No. of Cats	Frequency (%)
Presenting complaint		
Dermatologic disease	11	73
Lethargy	9	60
Poorly regulated DM	8	53
Clinical signs		
PU/PD	14	93
Weight loss	10	67
Lethargy	10	67
Polyphagia	5	33
Physical examination		
Dermal atrophy	12	80
Pendulous abdomen	8	53
Dermal wounds	8	53
Spontaneous alopecia	4	27
Comorbidities		
DM	9	60
Heart murmur (grades 1–4/6)[a]	8	53
Skin fragility syndrome	8	50
AP	2	13
Diabetic ketoacidosis	1	7
Gastrointestinal disease	1	7

HAC, hyperadrenocorticism; DM, diabetes mellitus; PU/PD, polyuria/polydipsia; AP, acute pancreatitis.
[a]One case had recurrent congestive heart failure.

Table 2. Tests performed to determine HAC diagnosis.

	No. of Cats (%)
Tests	
LDDST[a]	13 (87)
BA[b]	13 (87)
ACTH stimulation test (minutes)	5 (33)
0, 30, 60	2 (13)
0, 60, 90	1 (7)
0, 30, 60, 120	1 (7)
Unknown	1 (7)
Endogenous ACTH	2 (13)
UCCR	1 (7)
MRI (macroadenoma)	1 (7)
Diagnosis	
PDH	14 (93)
Left AT	1 (7)

AT, adrenal tumor; BA, bilateral adrenomegaly found on abdominal ultrasound; HAC, hyperadrenocorticism; LDDST, low-dose dexamethasone suppression test; PDH, pituitary-dependent hyperadrenocorticism; MRI, magnetic resonance imaging; UCCR, urinary cortisol : creatinine ratio.
[a]Dose of dexamethasone administered is unknown in 1 case.
[b]Follow-up abdominal ultrasound revealed BA in 1 case.

that are diabetic.[1] HAC was diagnosed based on failure to suppress circulating cortisol concentrations in a cat with compatible clinical signs.[11] Various other tests or combinations were performed (Table 2). ACTH stimulation testing was performed by administering 125 μg synthetic ACTH IV in 4 of 5 cases. The response was exaggerated if after 1 hour cortisol levels were >19 μg/dL.[12]

Of those tested with dexamethasone suppression, 10/13 cats were consistent with PDH and the others failed to differentiate between PDH and a cortisol-secreting adrenocortical tumor. Median time between DM diagnosis and HAC diagnosis was 271 days (range 77–665). A serum thyroxine concentration was not increased in 10/15 cats with poorly controlled diabetes or unexplained weight loss.

Clinical Outcome

Most cats (13/15) had an initial improvement in their clinical signs after starting trilostane therapy. Dermatologic changes improved after 2 weeks to 3 months, whereas signs of PU/PD or lethargy improved in 1–4 weeks. Endocrine testing results improved in 13 of 15 cats. Cats were rechecked within 1–6 weeks after starting trilostane therapy. ACTH stimulation testing was performed at 1–3 time points (some combination of 30, 60, 90, or 120 minutes) after administration of synthetic ACTH. In 7 cases, cortisol measurement was performed at baseline and 60 minutes post-ACTH administration. Of 11/15 cases, 7 had ACTH stimulation testing performed 4 hours posttrilostane administration, 4 had testing 4–6 hours post, and in 4 the timing was not recorded. Of those that had ACTH stimulation tests performed, 11/15 received 125 μg/cat IV, 2 received an unknown dosage, 1 received 11 μg/kg IM, and 1 received 23 mcg/kg with an unknown administration route.

Of the 9 cats with DM, insulin dose requirements decreased by 36% on average in 6 cats. One cat had an insulin dose requirement increase. DM remission did not occur. The most common type of insulin administered was glargine[b] in 4, porcine insulin zinc suspension[c] in 2, protamine zinc recombinant human insulin[d] in 2, and NPH[e] in 1. Insulin dose at the time of HAC diagnosis was 0.76 U/kg/dose (mean, 0.3–2.3 range). After instituting trilostane therapy, mean insulin dosages decreased to 0.54 U/kg/dose within an average of 55 days. All diabetics received twice daily insulin therapy. Insulin administration frequency did not change unless it was discontinued. One cat in diabetic remission at the time of HAC diagnosis remained in diabetic remission. Deceases in insulin doses were based on normal to near-normal serum fructosamine measurements in 3, spot blood glucose measurements with improved clinical signs in 2, and a glucose curve in 1.

Initial dosing of trilostane frequency was once daily for 13/15 cats. Dose adjustments were performed in 6 cases (Table 3). Five were switched to twice daily dosing. Times to first recheck ACTH stimulation testing

Table 3. Dosage adjustments and monitoring.

	No. of Cats (%)
Dose (mg q24h)	
10	8 (53)
30	5 (33)
20 mg q12h	1 (7)
10 mg q12h	1 (7)
No. of adjustments	
0	9 (60)
1	4 (27)
>5	2 (14)
Reason for adjustment	
Clinical signs, ACTH stim	4 (27)
Persistent hypernatremia	1 (7)
Unknown	1 (7)
No. of ACTH stim tests	
≥1 to ≤2	2 (13)
≥3 to ≤6	8 (53)
≥8 to ≤10	5 (33)

varied; however, 12/15 cats had a recheck within 3 weeks. Subsequent monitoring was performed a few weeks later (in 4), 1–2 months later (in 6), 4–6 months thereafter (in 4), and unknown in 1. The mean initial dose of trilostane was 4.3 mg/kg once daily and 3.3 mg/kg twice daily. The mean final dose of trilostane was 2.7 mg/kg once daily and 5.6 mg/kg twice daily.

Of the 9 cases euthanized 1 was lost to vehicular trauma, trilostane therapy ranged from 87 to 1,278 days with a median of 655 days. The cases without follow-up had received trilostane for at least 80, 252, 275, 711, and 829 days based on the date of last veterinary contact. Overall median survival time was 617 days (range 80–1,278).

Complications

Common complications included weight loss, followed by urinary tract infections (UTIs) (Table 4). Three of the 5 UTI cases had initial sonographic

Table 4. Outcomes and complications.

Outcome/Complications	No. of Cats (%)
Euthanasia	9 (60)
Weight loss	6 (40)
UTI	5 (33)
CKD	3 (20)
Lethargy	3 (20)
Alive	3 (20)
Seizures	2 (13)
Recurrent pancreatitis	2 (13)
Gastrointestinal small cell lymphoma	2 (13)
Lost to follow-up	2 (13)
Recurrent hypernatremia	1 (7)
Vehicular trauma	1 (7)

CKD, chronic kidney disease; UTI, urinary tract infection.

evidence of chronic kidney changes and also had DM. Another complication was the development of azotemia. Two of the 3 had initial sonographic evidence of chronic kidney changes. Of those with a recheck of serum BUN concentration following trilostane therapy, 3 had normalization, and 1 had a 50% decrease in serum BUN concentration, although the value was still moderately abnormal (44 mg/dL). Renal failure (RF) developed in 1 of the 5 imaged cases (with initial chronic kidney changes) with subsequent euthanasia thereafter. RF developed in 1 that did not have initial sonographic chronic kidney changes.

Two cases had complications from trilostane therapy. Cat 9 developed lethargy and anorexia. ACTH stimulation test results were subnormal. Reevaluation after a dose decrease revealed improved clinical signs and ACTH stimulation testing. Cat 6 developed a dull mentation with relevantly lower ACTH stimulation results (although not subnormal) compared with results before starting trilostane therapy which resolved upon decreasing the dose, although ACTH stimulation test results were increased. Frequent increases based on increased ACTH stimulation test results and persistent clinical signs ended with a final decrease in dose of both insulin and trilostane performed as a result of clinical signs consistent with hypocortisolemia, although this was not reflected in the ACTH stimulation results. The serum fructosamine concentration was normal. Causes of death are outlined in Table 4.

Discussion

This retrospective study indicates that trilostane is a viable, well-tolerated, medical treatment option for management of cats with HAC.

Clinicopathologic data were in agreement with previous studies, with the exception of an increased serum BUN concentration found more commonly in this study (7/15, 47%) than in prior reports (7/32, 22%).[1] Imaging studies of the kidneys in 4/7 of these cases identified changes consistent with chronic kidney disease (CKD). Given the catabolic effect of cortisol, concurrent muscle atrophy could have underestimated the degree of azotemia in these cats. In addition, although dietary history was not always recorded, at least 9 were consuming a diabetic diet, which is high in protein and can result in an increased BUN.

Endocrinopathies in association with DM include acromegaly, which might be difficult to distinguish from PDH in the absence of skin fragility syndrome. Measurement of IGF-1 was not performed in any of these cats; however, 8/15 of the cats in this case report were presented with skin fragility syndrome and had cortisol function testing results consistent with HAC. A prospective study evaluating plasma ACTH precursors in cats with PDH revealed that most cats had increased concentrations of plasma ACTH precursors, compared with healthy cats, or cats with DM with or without acromegaly.[13] Precursor measurement might aid in differentiating PDH

from acromegaly in conjunction with IGF-1 levels and clinical signs, if a suspected cushingoid cat does not have fragile skin.

In assessing tumor differentiation, 10 were consistent with PDH based on LDDST. This was somewhat unexpected, as many cats with PDH will not suppress 4 hours after dexamethasone administration and a few will suppress at 8 hours.[14] If combined with sonographic results of bilateral adrenomegaly, findings were consistent with PDH in 1 additional case. One had an adrenal tumor based on left unilateral adrenomegaly, with an atrophied contralateral AG. The remaining case identified unilateral adrenomegaly, with a normal-sized contralateral gland.

This study demonstrated clinical sign improvement in cats with HAC, consistent with previous studies.[9] As expected, dermatologic signs resolved more slowly than clinical signs of PU/PD and lethargy.[11] ACTH stimulation monitoring led to an improvement in results of tested cases.

The reduction in insulin dose seen in this study was in contrast to the previous report of 3 diabetic cats treated with trilostane for HAC, in which there was insufficient information to conclude if insulin requirements were reduced.[9] This is most likely secondary to a small sample size as 52% (11/21) of cats with long term follow up available that were treated successfully for HAC by means other than trilostane (other medical or surgical) had resolution of their DM. Other treatments included mitotane, metyrapone, or adrenalectomy (bilateral or unilateral).[1] In dogs, treatment is expected to alleviate insulin resistance, but resolution of DM is rare. The difference is likely secondary to reversible glucocorticoid-induced peripheral insulin resistance. Although dogs can develop transient DM secondary to an insulin antagonistic disorder (like HAC), these dogs are typically diagnosed with DM first. It is unknown which disorder develops first; given the multifactorial etiology of DM and the common finding of immune-mediated destruction of the pancreatic islet cells in dogs, resolution of DM is not expected. Cats often have a relevant population of residual functional beta cells at the time of DM diagnosis. Once the cause of insulin antagonism is addressed therapeutically, beta cell function should improve, depending on the chronicity.[15]

Trilostane doses in this study were lower when compared to previous studies with a mean initial dose of 4.3 mg/kg once daily (in 13), 3.3 mg/kg twice daily (2), and final dosages of 2.7 mg/kg once daily (8), 5.6 mg/kg twice daily (7), compared to a mean initial dose of 5.8 mg/kg once daily (5), and final dosages of 5.4 mg/kg once daily (2), 7 mg/kg twice daily (3) previously reported.[9] That study extrapolated the dose from a study of 78 dogs treated with once daily trilostane. Dogs weighing less than 5 kg received 30 mg trilostane once daily.[16] Studies using trilostane in cats have not been performed, necessitating extrapolation. The 1st case report published using trilostane in a cat with PDH started with 30 mg once daily and increased the frequency to 30 mg twice daily for complete skin lesion

resolution.[17] Studies in dogs have demonstrated equal to superior efficacy in using twice daily trilostane therapy.[f] [18–20]

In our study, 13/15 cases were initially started on a once daily therapy and 5 switched to twice daily therapy. Administration frequency changed because of increased ACTH stimulation test results in conjunction with persistent clinical signs. All those cases were diabetic and receiving twice daily insulin. Cats on twice daily insulin likely benefit from twice daily trilostane based on both drugs' duration of action and ease of owner administration/compliance.[21] As the pharmacokinetics and pharmacodynamics of trilostane remain unknown in cats, testing protocols and dosages should be optimized before making definitive recommendations.

Monitoring included ACTH stimulation testing 4–6 hours posttrilostane administration, which is similar to the manufacturer's recommendations for dogs under treatment for PDH.[a] A 3 hours nadir after trilostane administration in 1 cat was previously reported, justifying similar timing for ACTH stimulation testing as recommended in dogs.[9] Timing of post-ACTH serum cortisol measurements was varied, as cats have a peak serum cortisol response at different times with varying doses of synthetic ACTH.[22–24] Studies that have used the standard- (125 µg/cat) or low-dose ACTH stimulation test (5 µg/kg) have reported peak cortisol responses at 60 minutes in overweight or healthy purpose-bred cats.[25,26] Guidelines for monitoring dogs receiving trilostane for HAC include an ACTH stimulation test at 10–14, 30, and 90 days later and every 90 days thereafter.[a] Clinical signs and cortisol concentrations continue to improve in most dogs within the first month, therefore some authors advocate testing within the first 10–14 days without making adjustments until 30 days of trilostane therapy.[11,21] Based on this study and previous studies, monitoring via ACTH stimulation testing (5 µg/kg IV) 10–14 days later (4–6 hours after trilostane administration), along with monitoring weight, clinical signs, electrolytes, and glucose is recommended, followed by reevaluations on day 30 and 90, and every 90 days thereafter. It is also important to remember that trilostane therapy in dogs leads to adrenomegaly consistent with diffuse hyperplasia, nodular hyperplasia, or both, likely due to the loss of negative feedback as a result of lowering cortisol production, leading to excessive ACTH production, a direct action of trilostane or its metabolites.[27,28] To the authors' knowledge, this has not been studied in cats yet.

Duration of treatment was variable. The shortest survival time was 87 days. This case had multiple recurrent episodes of hypernatremia (including at the time of HAC diagnosis) and a declining quality of life. Therefore, euthanasia was elected.

Causes of hypernatremia were not definitively established; however, renal losses of pure water or hypothalamic disorders seem likely. This cat had a diagnosis of PDH, though no advanced imaging was performed and had chronic kidney changes evident on initial ultrasonographic examination, making a renal disorder, hypothalamic disorder, or both a likely cause of the observed hypernatremia.

Nelson's syndrome can occur in humans and some dogs, from rapid enlargement of a pituitary mass after loss of negative feedback from adrenal cortisol production (via surgical or medical treatment).[29] Common clinical signs associated with pituitary tumors in cats are blindness, altered consciousness, lethargy, and anorexia.[30] In this study, no cats had any reports of blindness; however, the shortest surviving case was lethargic, anorexic, and adipsic. Advanced diagnostic imaging was only performed in 1 cat in this series. That cat had evidence of a pituitary macroadenoma, surviving 750 days on trilostane, and ultimately was euthanized and diagnosed with small cell lymphoma of the gastrointestinal tract based on necropsy examination, with clinical signs of anorexia and weight loss at the time of euthanasia.

Adverse effects of trilostane administration in dogs with HAC include adrenal necrosis, hypoadrenocorticism, and hyperkalemia.[28] RF and weight loss are important adverse effects in cats.[9] Weight loss was reversible upon decreasing the dose of trilostane. RF was determined to be the most likely cause of death; however, it was not clear whether it was a direct effect of the trilostane or owing to a concurrent disorder, as RF is common in older cats and occurs in conjunction with HAC and DM.[5] A prospective study comparing renal function of dogs diagnosed with PDH and treated with trilostane or transsphenoidal hypophysectomy demonstrated an important decline in GFR 1 year after treatment, with increased GFRs noted before treatment, with no development of azotemia.[31]

In our study, common complications were weight loss and UTIs. UTIs could be secondary to DM, CKD, HAC, or all the three. Another complication was the development of azotemia, which could be secondary to progression of CKD as most (2/3) had evidence of chronic kidney changes on initial ultrasonographic examination. This was progressive in 1 case, being the ultimate cause of euthanasia after 570 days of trilostane therapy.

Manufacturers do not recommend trilostane therapy if hepatic disease, renal insufficiency, or both is present. A direct relationship with trilostane therapy causing weight loss was not identified. Other important complications include anorexia, lethargy, recurrent pancreatitis, recurrent hypernatremia, lymphoma, and seizures. Existence of these complications highlights the need for diligent monitoring of these cats. Their comorbidities make direct causation from trilostane nearly impossible to prove. Recognizing signs of hypocortisolemia in cats is important, with signs of lethargy, anorexia, and weight loss reported. Clinicopathologic findings of hypocortisolemia can be more difficult to determine, as the classic electrolyte abnormalities associated with hypoaldosteronism are not present or may not actually reflect a lack of aldosterone; however, hypoglycemia or absence of a stress leukogram may increase hypocortisolism suspicion, illustrating how important it is to perform an ACTH stimulation test.[32,33]

There are several study limitations. The retrospective nature and small sample size make sweeping claims regarding the efficacy of trilostane therapy in cats with HAC difficult. As HAC is infrequently diagnosed, prospective studies remain unlikely.

In conclusion, through retrospective analysis, trilostane ameliorates clinical signs of HAC in cats, is well tolerated long term, and can lead to improved glycemic control in the majority (67%) of cases.

Footnotes

Acknowledgments

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