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A Comparison of Factors that Influence Survival in Dogs with Adrenal-Dependent Hyperadrenocorticism Treated with Mitotane or Trilostane

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Background: Trilostane is a recognized treatment for canine pituitary-dependent hyperadrenocorticism (PDH); however, its efficacy in dogs with adrenal-dependent hyperadrenocorticism (ADH) is unknown.

Objectives: To examine factors that might influence survival in the medical management of ADH, with particular emphasis on treatment selection.

Animals: Thirty-seven animals referred to 4 centers over a period of 12 years that had been diagnosed with ADH and treated with either trilostane (22/37), mitotane (13/37), or both (2/37).

Methods: Retrospective analysis of clinical records.

Results: There was no statistically significant difference between the survival times of 13 dogs treated only with mitotane when compared with 22 dogs treated only with trilostane. The median survival time for animals treated with trilostane was 353 days (95% confidence interval [CI] 95–528 days), whereas it was 102 days (95% CI 43–277 days) for mitotane. Metastatic disease was detected in 8 of 37 dogs. There was a significantly lower probability of survival for dogs with metastatic disease when compared with those without metastatic disease ($P < .001$).

Conclusions and Clinical Importance: The choice of medical treatment for ADH may not have a major effect on survival times. However, the presence of metastatic disease considerably decreases survival time regardless of the choice of medical treatment.

Key words: Adrenal; Cushings; Endocrine; Treatment.

Spontaneously occurring hyperadrenocorticism (HAC) may be associated with inappropriate secretion of ACTH from the pituitary gland (pituitary-dependent hyperadrenocorticism [PDH]) or a primary adrenal disorder (adrenal-dependent hyperadrenocorticism [ADH]). ADH is responsible for approximately 15% of all cases of HAC and may be because of an adrenal adenoma or carcinoma.[1]

Mitotane (op DDD) is a DDT derivative with cytotoxic effects on the adrenal cortex (zona reticularis and zona fasciculata) and was the most common treatment for PDH in Europe and the United States.[2] Trilostane (4,5-epoxy-17-hydroxy-3-oxoandrostan-2-carbonitrile) is a synthetic nonhormonal steroid and a competitive inhibitor of 3-β-hydroxysteroiddehydrogenase.[3] Therefore, mitotane is considered an adrenocorticolytic drug, whereas trilostane is adrenocorticostatic. The clinical use of trilostane in canine PDH has been reported by several groups,[4–9] and these studies have been reviewed elsewhere.[10]

The reported median survival times for dogs with PDH treated with trilostane range from 662 to 900 days and 708 to 720 days for those treated with mitotane.[11,12] There was only a significant difference between survival times in relation to treatment in the 2nd study,[12] although treatment protocols varied between the 2 reports.

Mitotane also has been the mainstay of medical treatment for ADH. The reported median survival time with this treatment is approximately 320 days.[13] Only 1 small series and 2 case reports have been published on the use of trilostane in canine ADH.[14–16] The 1st case survived more than 560 days[14] and the 2nd case survived for 117 days.[16] A series of 3 dogs with adrenal tumors and metastatic disease survived for 295, 342, and 506 days.[15]

Abbreviations:

ADH	adrenal-dependent hyperadrenocorticism
CI	confidence interval
CNS	central nervous system
HAC	hyperadrenocorticism
HR	hazard ratio
17OHP	17-hydroxyprogesterone
LDDST	low-dose dexamethasone suppression test
PDH	pituitary-dependent hyperadrenocorticism
UCCR	urine corticoid creatinine ratio

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There have been no large studies that have reported the median survival times of dogs with ADH treated with trilostane and compared these dogs with a similar group of dogs treated with mitotane. Therefore, the aim of this study was to compare factors that may be associated with survival time after diagnosis of ADH and medical treatment with mitotane or trilostane or both.

Materials and Methods

Clinical Cases

Medical records for all dogs diagnosed with ADH at each of the 4 referral-only hospitals, from January 1, 1996 to December 1, 2008, were reviewed. The centers involved were the Small Animal Hospital of the University of Glasgow (Center 1), Davies Veterinary Specialists (Center 2), University of Bristol Small Animal Hospital (Center 3), and Queens Veterinary School Hospital of the University of Cambridge (Center 4). Only animals treated medically for ADH with mitotane,[a] trilostane,[b] or a combination of both and had sufficient case records available were included. Animals that had not been treated or had been managed surgically were excluded.

Each veterinary center performed a retrospective review of medical records by searching their databases for cases using the key words "mitotane" and "trilostane" and their imaging databases also were searched for the key words "adrenal mass," "adrenal enlargement" or "hyperadrenocorticism (Cushing's)." The case files were reviewed directly to distinguish between PDH and ADH.

Data obtained from the records included breed, sex, date of birth, weight and age at diagnosis, date of diagnosis, treatment given, and date of treatment initiation. Date of death or survival to June 1, 2008, also was recorded. When necessary, referring veterinarians, owners, or both were contacted. The results of pretreatment ACTH stimulation tests, low-dose dexamethasone suppression tests (LDDSTs), 17-hydroxyprogesterone (17OHP) assays, urine corticoid : creatinine ratios (UCCR), endogenous ACTH plasma concentration assays, abdominal ultrasonography, thoracic radiography, and histopathology (ante- or postmortem) also were recorded.

Diagnosis of HAC

Each center used similar diagnostic protocols. Suspicion of HAC was based on history, clinical examination, and routine blood analysis. An ACTH stimulation test was performed as described elsewhere.[17] HAC was confirmed if there was an exaggerated increase in circulating cortisol concentration (> 600 nmol/L or 21.6 g/dL) 1 hour post-IV administration of synthetic tetracosactide.[c] In animals with clinical signs and biochemical markers of HAC but without a positive ACTH stimulation test, diagnosis was confirmed if a LDDST demonstrated inadequate suppression (> 40 nmol/L or 1.44 μg/dL) of cortisol concentration 8 hours after IV administration of a low dose of dexamethasone.[d] Cortisol was measured by external commercial laboratories by radioimmunoassays or immunoradiometric assays validated for use in the dog, with appropriate quality controls.

Cases that had an inverse LDDST pattern with < 50% suppression at 3 hours[18] also were included if they also had a compatible UCCR. The test that confirmed the diagnosis was recorded for later analysis.

Confirmation of ADH

HAC was diagnosed as being adrenal dependent (ADH) in almost all cases by a combination of low endogenous ACTH concentration (< 5 ng/ml) and abdominal ultrasonography findings (indicative of unilateral adrenal enlargement) as described previously.[19] Cases also were included if they had a diagnosis of HAC and a single large calcified (> 10 mm) adrenal gland when examined with abdominal ultrasonography or radiography[14] and responded to trilostane or mitotane treatment. Additionally, cases that had a diagnosis of HAC and an adrenal adenoma or carcinoma confirmed by histopathology also were included.

Blood to measure endogenous ACTH was collected as described previously.[19] Briefly, blood was collected into a cooled EDTA tube on ice, centrifuged immediately at 1,500 × *g* for 10 minutes, and the plasma frozen at −20°C. The frozen plasma was sent in a cold pack to a single commercial laboratory, where it was analyzed by an immunoradiometric assay[e] that had been validated for use in dogs.[20]

All patients had abdominal ultrasonography to evaluate for blood vessel invasion by the adrenal mass. Tumor staging was based on the findings of abdominal ultrasonography and, when available, thoracic radiography.

Histopathology was classified as either benign (adenoma) or malignant (carcinoma). Criteria for the classification of a carcinoma were histopathological evidence of invasive behavior. This included vascular invasion, high mitotic rate (evaluated over 10 high power fields), increased nuclear pleomorphism, a high percentage of tumor necrosis, or some combination of these findings.

Concurrent disease at presentation as detected by clinical examination, CBCs, biochemistry profiles, and imaging modalities were recorded for all cases. It was also noted if additional concurrent diseases were present within 1 month of diagnosis of ADH or if the concurrent disease developed later.

Treatment Regimen

The same treatment protocol was used for each drug at each center.

Mitotane treatment involved an induction period followed by a maintenance dose.[13,21] During the induction period, mitotane was administered at a dosage of 50 mg/kg, up to a maximum of 1,000 mg/dog, until polyphagia or polydipsia resolved and the post-ACTH cortisol concentration was < 120 nmol/L or 4.32 μg/dL.[21] After successful induction, a maintenance dose of mitotane was given (initially 50 mg/kg/wk). The aim was to achieve a postmedication post-ACTH stimulation test cortisol concentration of < 120 nmol/L or 4.32 μg/dL.[21] At the end of induction and during the maintenance phase, a good clinical response to treatment was defined as a reduction or elimination of polyphagia and polydipsia and return of normal coat quality with minimal adverse effects. Mitotane maintenance doses were adjusted in amount or frequency to achieve these aims in individual animals.

Trilostane treatment did not involve an induction period. The starting doses of trilostane were those recommended by the manufacturer's UK data sheet and were based on body weight (and available capsule size): < 5 kg: 30 mg, 5.1–20 kg: 60 mg, 21–40 kg: 120 mg, and > 40 kg: 120–240 mg. All starting doses were administered orally once daily.[4] Trilostane 10 mg capsules were not available during the study period.

All dogs had an ACTH stimulation test performed within 1–2 weeks of starting trilostane, a second performed between 4 and 6 weeks, and a third at 10–14 weeks. If the patient remained stable, monitoring with ACTH stimulation tests then was undertaken every 3 months, as per the drug datasheet.

The aim of treatment was to achieve a post-ACTH stimulation test cortisol concentration within the range 40–150 nmol/L or 1.44–4.32 μg/dL in an ACTH stimulation test performed 4 hours postmedication[5,6,9,10] with good clinical control of HAC. The initial dose and frequency of administration were adjusted accordingly to achieve these goals. However, dose adjustments were not necessarily made in those dogs that had a postmedication post-ACTH stimulation test cortisol concentration of 150–200 nmol/L (4.32–7.2 μg/dL) but with clinical signs that had responded well to treatment.

Excessive clinical control was defined as clinical signs of hypoadrenocorticism and a post-ACTH cortisol concentration <40 nmol/L. Treatment was temporarily discontinued if patients showed clinical signs or serum electrolyte concentrations consistent with hypoadrenocorticism. When these signs had resolved, the dogs were started back on treatment at a lower dosage. Animals with a post-ACTH stimulation cortisol concentration <40 nmol/L but without clinical signs of hypocortisolism were monitored more frequently.

Statistics

Descriptive Statistics. Population attributes treated as continuous data (age at diagnosis and weight) of the dogs in the 4 centers were assessed for normality and compared among veterinary centers by a Kruskall-Wallis test (comparisons among centers) or Mann-Whitney (Wilcoxon rank sum) test (comparisons between drug treatments) for nonparametric data. Other population attributes that were treated as categorical data (including age at diagnosis, weight, breed, reproductive status, sex, and the presence of concurrent disease) were compared by Fisher's exact-test (differences between drug treatments).

Survival Analysis. Survival analysis (survival in days from date of drug treatment) was performed by a Kaplan-Meier product limit method. Log-rank, Wilcoxon, Tarone-Ware, and Peto-Peto Prentice tests were used to determine whether the overall survival functions in 2 or more groups were equal.[22] Median and mean survival times for important variables were calculated. This approach was supplemented with a Cox proportional hazards model. Potential predictor variables included method of diagnosis, drug treatment (mitotane compared with trilostane), veterinary center (Center 1, 2, 3, or 4), breed group (Table 3), reproductive status (intact or neutered), sex (female or male), age at diagnosis, weight at diagnosis, presence or absence of blood vessel invasion, presence or absence of concurrent disease (within 1 month of study start date), and presence or absence of metastatic disease. Reproductive status also was considered as a polytomous categorical variable (female intact, female neutered, male intact, male neutered). Age and weight were considered as continuous, categorical, and binary variables, based on median values (age: ≤11 years, >11 years; weight: ≤27.4 kg, >27.4 kg).

Univariable Cox proportional hazards regression analyses were performed to screen potential predictors for subsequent inclusion in a multivariable model. Variables with a P value ≤ .25 were considered for inclusion in the final model-building process. A full model containing all variables was produced. Variables then were removed one at a time until the model with the best fit was identified. Potential for confounding between variables was assessed. Biologically plausible interaction terms were assessed but not included in the final model because of the small number of observations in the study. The proportional hazards assumption was tested for each variable in the model by examination of Schoenfield residuals and graphical techniques. Further model diagnostics were performed to identify outliers and influential points.[22]

All analyses were carried out by Stata 10 statistical software.[f] Statistical significance was set at $P < .05$ for all tests. Power calculations were performed and it was determined that in order to achieve 80% power to detect a hazard ratio (HR) of ≥2, assuming a 5% level of significance, 132 animals (66 animals in each treatment group) would be required. In contrast, to detect an HR of ≥5, 26 animals (13 in each group) would be adequate.

Results

Fifty-six cases were retrieved from the records. Only 37 dogs fulfilled all of the inclusion criteria and were included in the study. Seven cases were excluded because of an inconsistent ACTH assay (>5 ng/mL) and the adrenal mass was <10 mm in diameter, 5 cases were excluded because they had minimal adrenomegaly (or inconclusive imaging findings on review, including bilateral adrenomegaly) and an ACTH assay was not performed, 6 cases were excluded because a diagnosis of HAC was not confirmed (although all had adrenal tumors), and 1 case that received both trilostane and mitotane also had a partial adrenalectomy and therefore was excluded. In all cases that were included, the contra-lateral adrenal gland either was not detected or was <7 mm diameter when examined by ultrasonography. All cases of bilateral adrenomegaly were excluded (even though it is possible that some of these dogs may have had bilateral adrenal tumors).

The diagnosis of HAC was made in 36 of 37 dogs on the basis of an exaggerated response after an ACTH stimulation test, failure to suppress cortisol concentrations after a LDDST or both. One case had a reverse LDDST[18] and a compatible UCCR. All 37 cases had a diagnosis of HAC and an adrenal ultrasound examination that demonstrated the presence of a unilateral adrenal mass >10 mm. Thirty-one of 37 had an ACTH concentration <5 ng/mL. In the remaining 6 dogs, the diagnosis of ADH was based on histopathology confirming an adrenal carcinoma (in 2 dogs) or unequivocal clinical signs, unilateral adrenomegaly (>10 mm) and response to treatment (in 4 dogs).

Thirty-six dogs died before the end of the study. The one that survived was still alive at the time of manuscript submission.

Of the 37 dogs included in the study, 13 patients came from Center 1, 7 patients from Center 2, 5 patients from Center 3, and 12 patients from Center 4. Although there was a significant difference in the drug treatment regimens preferred by the different centers ($P = .004$), the diagnostic techniques used to confirm HAC and diagnose ADH were the same (Table 1) and there were no significant differences among the age, sex, and breeds of the dogs (Tables 2 and 3).

There were 37 dogs treated by medical management: 13 with mitotane, 22 with trilostane, and 2 with mitotane then trilostane. No dogs were treated with mitotane and trilostane concurrently. The 2 dogs treated with mitotane and trilostane were excluded from comparisons involving treatment groups.

There were no significant differences among the dogs in each treatment group when comparing population measures and clinical findings (Tables 3 and 4).

There is evidence of a temporal relationship with relation to drug choice. Although from 1996 to 1998 all dogs were treated with mitotane (6/6), between 1998 and 2001 both products were available. In this time period, 8 dogs were treated with trilostane, 6 with mitotane, and 1 with both drugs. From 2002, 14 dogs were treated with trilostane (because this was the UK veterinary-licensed

Table 1. Distribution of drug treatment and diagnostic regimen by veterinary center.

Variables	Center 1	Center 2	Center 3	Center 4	Total	*P*-Value
Drug treatment regimen						
Mitotane	3 (23%)	0 (0%)	0 (0%)	10 (83.3%)	13 (35.1%)	.004
Trilostane	9 (69%)	7 (100%)	4 (80%)	2 (16.7%)	22 (59.5%)	
Both	1 (8%)	0 (0%)	1 (20%)	0 (0%)	2 (5.4%)	
Total	13 (100%)	7 (100%)	5 (100%)	12 (100%)	37 (100%)	
Diagnostic regimen						
ACTH stimulation test						
Performed	13 (100%)	7 (100%)	4 (80%)	12 (100%)	36 (97.3%)	.92
Not performed	0 (0%)	0 (0%)	1 (20%)	0 (0%)	1 (2.7%)	
Total	13 (100%)	7 (100%)	5 (100%)	12 (100%)	37 (100%)	
LDDST						
Not performed	2 (15.4%)	2 (28.6%)	1 (20%)	3 (25%)	8 (21.6%)	.96
Performed	11 (84.6%)	5 (71.4%)	4 (80%)	9 (75%)	29 (78.4%)	
Total	13 (100%)	7 (100%)	5 (100%)	12 (100%)	37 (100%)	
ACTH						
Not performed	0 (0%)	2 (28.6%)	2 (40%)	2 (16.7%)	6 (16.2%)	.54
Performed	13 (100%)	5 (71.4%)	3 (60%)	10 (83.3%)	31 (83.8%)	
Total	13 (100%)	7 (100%)	5 (100%)	12 (100%)	37 (100%)	
UCCR						
Not performed	12 (7.7%)	6 (85.7%)	4 (80%)	12 (100%)	34 (91.9%)	.89
Performed	1 (92.3%)	1 (14.3%)	1 (20%)	0 (0%)	3 (8.1%)	
Total	13 (100%)	7 (100%)	5 (100%)	12 (100%)	37 (100%)	
Pre/post-17OHP						
Not performed	13 (100%)	7 (100%)	4 (80%)	10 (83.3%)	34 (91.9%)	.84
Performed	0 (0%)	0 (0%)	1 (20%)	2 (16.7%)	3 (8.1%)	
Total	13 (100%)	7 (100%)	5 (100%)	12 (100%)	37 (100%)	
Abdominal ultrasound						
Performed	13 (100%)	7 (100%)	5 (100%)	12 (100%)	37 (100%)	ND
Total	13 (100%)	7 (100%)	5 (100%)	12 (100%)	37 (100%)	
Thoracic radiography						
Not performed	0 (0%)	2 (28.6%)	0 (0%)	0 (0%)	2 (5.41%)	.72
Performed	13 (100%)	5 (71.4%)	5 (100%)	12 (100%)	35 (94.59%)	
Total	13 (100%)	7 (100%)	5 (100%)	12 (100%)	37 (100%)	
Advanced imaging						
Not performed	13 (100%)	7 (100%)	5 (100%)	12 (100%)	37 (100%)	ND
Total	13 (100%)	7 (100%)	5 (100%)	12 (100%)	37 (100%)	
Histopathology						
Not performed	10 (76.9%)	6 (85.7%)	5 (100%)	11 (91.7%)	32 (86.5%)	.87
Performed	3 (23.1%)	1 (14.3%)	0 (0%)	1 (8.3%)	5 (13.5%)	
Total	13 (100%)	7 (100%)	5 (100%)	12 (100%)	37 (100%)	

There was a significant difference between choice of drug treatment and center.

ND, not done; *P*-value not calculated.

ADH, adrenal-dependent hyperadrenocorticism; 17OHP, 17-hydroxyprogesterone; LDDST, low-dose dexamethasone suppression test; UCCR, urine corticoid creatinine ratio.

product from 2005), only 1 with mitotane and 1 with both drugs. If time of treatment is converted into a binary outcome (before 2002 and 2002 or later), mitotane was 21 (95% confidence interval [CI] 2.29–192.81) times more likely than trilostane to be used before the year 2002. When the presence of metastatic disease was accounted for in this analysis, it was not significantly associated with time of treatment or with the choice of drug treatment.

Median age at diagnosis was 11 years (mean, 11.5; standard deviation [SD], 1.87; range 7–14 years). Median weight at diagnosis was 26 kg (mean, 25.5; SD, 13.2; range 3.2–63 kg). There were 24 female dogs. Of these, 7 were intact and 17 were neutered. There were 13 male dogs. Of these, 6 were intact and 7 were neutered. There were 14 breeds represented: 8 Labradors, 2 Labrador cross breeds, 4 Yorkshire Terriers, 4 Boxers, 2 English Springer Spaniels, 2 Jack Russell Terriers, 1 each of Pyrenean Mountain Dog, Fox Terrier, Scottish Terrier, Hungarian Vizsla, German Shepherd Dog, Irish Setter, Rough-Haired Collie, and Border Collie, and 7 crossbreed dogs.

Two dogs had concurrent disease either at presentation or within 1 month of diagnosis (1 had a Leydig tumor and the other had pancreatitis and pyelonephritis). During the course of treatment, 9 more dogs were recorded as developing concurrent disease. Three dogs had signs of cardiac disease and were managed with angiotensin converting enzyme inhibitors and furosemide, one dog had surgically managed pyometra,

Table 2. Distribution of the clinical findings in dogs with ADH by veterinary center.

Variables	Center 1	Center 2	Center 3	Center 4	Total	*P*-Values
Invasion of blood vessels						
Not detected	13 (100%)	5 (71.4%)	3 (60%)	11 (91.7%)	32 (86.5%)	.52
Present	0 (0%)	2 (28.6%)	2 (40%)	1 (8.3%)	5 (13.5%)	
Total	13 (100%)	7 (100%)	5 (100%)	12 (100%)	37 (100%)	
Concurrent disease (at any point from diagnosis)						
Not detected	7 (53.8%)	4 (57.1%)	3 (60%)	12 (100%)	26 (70.3%)	.20
Present	6 (46.2%)	3 (42.9%)	2 (40%)	0 (0%)	11 (29.7%)	
Total	13 (100%)	7 (100%)	5 (100%)	12 (100%)	37 (100%)	
Presence of metastatic disease						
Not detected	11 (84.6%)	4 (57.1%)	4 (80%)	8 (66.6%)	27 (73%)	.89
Present	2 (15.4%)	1 (14.3%)	1 (20%)	4 (33.3%)	8 (21.6%)	
Missing (ie, not recorded)	0 (0%)	2 (28.6%)	0 (0%)	0 (0%)	2 (5.4%)	
Total	13 (100%)	7 (100%)	5 (100%)	12 (100%)	37 (100%)	

There were no significant intercenter differences between frequencies of blood vessel invasion or presence of concurrent or metastatic disease.

1 dog developed chronic renal failure, 2 dogs had mammary neoplasia, 1 dog developed signs of spinal cord disease, and 1 dog had neurological signs consistent with a central nervous system (CNS) space-occupying lesion. Therefore, 11 of 37 dogs had concurrent disease overall. Of these dogs, 8 were treated with trilostane, 3 with mitotane, and none with both trilostane and mitotane (Table 4).

Histopathology results were available in 5 dogs. Three had a postmortem examination and all dogs had unilateral adrenal carcinomas (2 left and 1 right). Two dogs had antimortem biopsies, which confirmed unilateral adrenocortical carcinoma in both. Three of these dogs were treated with mitotane, 1 with trilostane and 1 with both. The finding of adrenal malignancy was not significant between groups ($P = .88$), although sample size was very small.

Of the 36 animals that were dead at date of censorship, 25 were euthanized. In 19 dogs, the cause of death or reason for euthanasia was recorded; however, in only some cases were postmortem examinations performed. Two dogs died of causes that were felt to be because of the ADH or its treatment. Of these 2 dogs, 1 dog died of metastatic neoplasia and the other of suspected hypoadrenocorticism (a reported adverse effect of both mitotane and trilostane treatment). An additional 8 of the 19 dogs died of causes that were felt potentially could have been because of ADH or its treatment. These included signs of collapse, progressive deterioration, poor quality of life, and what was described as ''old age.'' An additional 9 of the 19 dogs died of causes that were thought not be directly attributable to ADH or its treatment (eg, heart failure, tracheal collapse, CNS disease, and an infected mammary mass). In the remaining 17 animals, a reason for death was not recorded. It was felt that the data insufficiently reliable to compare the causes of death between the treatment groups or with the length of survival. However, no trends were apparent on visual inspection of the data.

Table 3. Distribution of population measures by veterinary center and by drug treatment regimen.

Variables	Center 1	Center 2	Center 3	Center 4	Total	*P*-Value	Mitotane	Trilostane	Both	Total	Fisher's Exact *P*-Value (Mann-Whitney's *P*-Value)
Total	13 (100%)	7 (100%)	5 (100%)	12 (100%)	37 (100%)		13 (100%)	22 (100%)	2 (100%)	37 (100%)	
Reproductive status (neutered)											
No	7 (53.8%)	1 (14.3%)	3 (60%)	2 (16.7%)	13 (35.14%)	.23	3 (23.08%)	10 (45.45%)	0 (0%)	13 (35.14%)	.28
Yes	6 (46.2%)	6 (85.7%)	2 (40%)	10 (83.3%)	24 (64.86%)		10 (76.92%)	12 (55.55%)	2 (100%)	24 (64.86%)	
Total	13 (100%)	7 (100%)	5 (100%)	12 (100%)	37 (100%)		13 (100%)	22 (100%)	2 (100%)	37 (100%)	
Gender											
Female	7 (53.8%)	5 (71.4%)	3 (60%)	9 (75%)	24 (64.86%)	.81	9 (69.23%)	14 (63.64%)	1 (50%)	24 (64.86%)	1
Male	6 (46.2%)	2 (28.6%)	2 (40%)	3 (25%)	13 (35.14%)		4 (30.77%)	8 (36.36%)	1 (50%)	13 (35.14%)	
Total	13 (100%)	7 (100%)	5 (100%)	12 (100%)	37 (100%)		13 (100%)	22 (100%)	2 (100%)	37 (100%)	
Age (years)											
≤11	6 (46.2%)	3 (42.86%)	3 (60%)	6 (50%)	18 (48.65%)	.96	7 (53.8%)	11 (50%)	0 (0%)	18 (48.65%)	1 (.76)
>11	7 (53.8%)	4 (57.14%)	2 (40%)	6 (50%)	19 (51.35%)		6 (46.2%)	11 (50%)	2 (100%)	19 (51.35%)	
Total	13 (100%)	7 (100%)	5 (100%)	12 (100%)	37 (100%)		13 (100%)	22 (100%)	2 (100%)	37 (100%)	
Weight (kg)											
≤27.4	8 (61.54%)	5 (71.4%)	3 (60%)	5 (41.67%)	21 (56.76%)	.72	6 (46.2%)	13 (59.09%)	2 (100%)	21 (56.76%)	.5 (.48)
>27.4	5 (38.46%)	2 (28.6%)	2 (40%)	7 (58.33%)	16 (43.24%)		7 (53.8%)	9 (40.91%)	0 (0%)	16 (43.24%)	
Total	13 (100%)	7 (100%)	5 (100%)	12 (100%)	37 (100%)		13 (100%)	22 (100%)	2 (100%)	37 (100%)	

Note that the Fisher's exact-test excluded the 2 dogs that had both mitotane and trilostane.

There were no significant differences in population measures between centers or drug treatment.

Table 4. Distribution of the clinical findings in dogs with ADH by drug treatment.

Variables	Mitotane	Trilostane	Both	Total	*P*-Values
Invasion of blood vessels					
Not detected	12 (92.3%)	18 (81.82%)	2 (100%)	32 (86.5%)	.83
Present	1 (7.7%)	4 (18.18%)	0 (0%)	5 (13.5%)	
Total	13 (100%)	22 (100%)	2 (100%)	37 (100%)	
Concurrent disease (at any point from diagnosis)					
Not detected	10 (76.9%)	14 (65%)	2 (100%)	26 (70.3%)	.45
Present	3 (23.1%)	8 (35%)	0 (0%)	11 (29.7%)	
Total	13 (100%)	22 (100%)	2 (100%)	37 (100%)	
Presence of metastatic disease					
Not detected	9 (69.23%)	17(77.27%)	1 (50%)	27 (72.97%)	.37
Present	4 (30.77%)	3 (13.64%)	1 (50%)	8 (21.62%)	
Missing (ie, not recorded)	0 (0%)	2 (9.09%)	0 (0%)	2 (5.41%)	
Total	13 (100%)	22 (100%)	2 (100%)	37 (100%)	
Histopathology					
Not performed	10 (76.9%)	21 (95.45%)	1 (50%)	32 (86.5%)	.88
Performed	3 (23.1%)	1 (4.55%)	1 (50%)	5 (13.5%)	
Total	13 (100%)	22 (100%)	2 (100%)	37 (100%)	
Confirmed carcinoma					
No	10 (76.9%)	21 (95.45%)	1 (50%)	32 (86.5%)	.88
Yes	3 (23.1%)	1 (4.55%)	1 (50%)	5 (13.5%)	
Total	13 (100%)	22 (100%)	2 (100%)	37 (100%)	

There were no significant interdrug differences between frequencies of blood vessel invasion, histopathological examination (confirmation of a carcinoma), or presence of concurrent or metastatic disease.

Kaplan-Meier Survival Estimates

The median survival time for all dogs from treatment was 277 days (95% CI, 102–473 days). Survival times for dogs in the study population ranged from 4 to 1,341 days. Treatment occurred fairly soon after diagnosis (median, 11 days; 95% CI, 6–16 days) in all but 1 case. One dog had an extended time from diagnosis to the start of treatment (174 days).

All variables were examined for an effect on survival rates. These statistical tests assumed that the ratio of risk of death for each group was constant across all strata.[22] There was no statistically significant difference between drug treatments. The presence of metastatic disease was the only variable that had an important and significant effect on survival time.

There was no significant difference between survival times of dogs (n = 35) treated with either mitotane or trilostane (*P* values: log-rank, .15; Wilcoxon, .12; Tarone-Ware, .13; and Peto-Peto, .12; Fig 1). However, the survivorship functions for each treatment crossed over which implied that the survival outcome for each drug treatment may have varied over time.[22] At the date of censorship, all dogs treated with mitotane were dead. The median survival time for dogs on mitotane (n = 13) was 102 days (95% CI, 43–277 days). The median survival time for dogs on trilostane (n = 22) was 353 days (95% CI, 95–528 days). The 1-year survival fraction for dogs on mitotane was 23% (95% CI, 5.6–47.5%), whereas the 1-year survival fraction for dogs on trilostane was 50% (95% CI, 28.2–68.4%).

All dogs had abdominal ultrasonography and all but 2 also had thoracic radiography for staging. Metastatic disease was detected in 8 of the 37 dogs and not detected in 27 dogs. There were 2 dogs for which the presence or absence of metastatic disease was not recorded, and these dogs were excluded from further analysis. Dogs without detected metastatic disease survived longer than those with metastatic disease (*P* values: log-rank, <.001; Wilcoxon, <.001; Tarone-Ware, <.001; and Peto-Peto, <.001; Fig 2). The median survival time for those dogs without detected metastatic disease was 402 days (95% CI, 163–531 days). The median survival time for dogs with metastatic disease was 61 days (95% CI, 4–172 days). The 1-year survival fraction for dogs without detected metastatic disease was 51.8% (95% CI, 31.9–

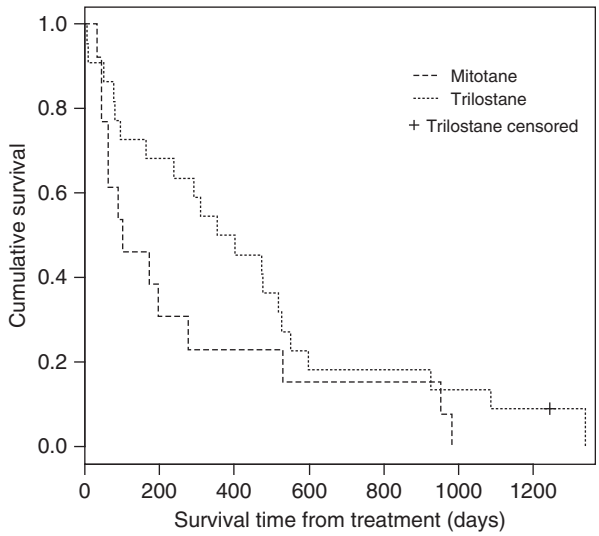

Fig 1. Kaplan-Meier survival curve for both mitotane- and trilostane-treated dogs (n = 35). Dogs alive at the completion of the study and those lost to follow-up were censored. The 2 dogs treated with both mitotane and trilostane were excluded from this analysis.

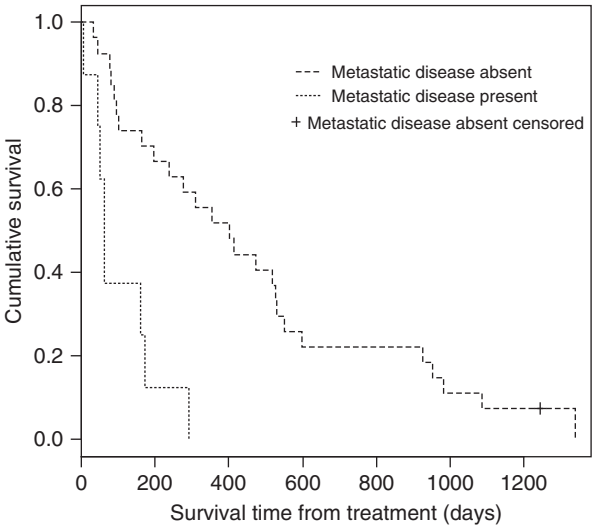

Fig 2. Kaplan-Meier survival curve for dogs (n = 35) with and without metastatic disease. Dogs alive at the completion of the study and those lost to follow-up were censored. There were 2 dogs for which the presence or absence of metastatic disease was not reported and these dogs were excluded.

68.6%). The 2-year survival fraction was 22.2% (95% CI, 9.0–39.0%). The 2-month survival fraction for the dogs with detected metastatic disease was 50% (95% CI, 15.2–77.5%), the 6-month survival fraction was 12.5% (95% CI, 0.7–42.3%) and 1-year survival fraction was 0%. Of the 8 dogs with detected metastatic disease, 4 were treated with mitotane, 3 with trilostane, and 1 with both. There was no significant difference between the dogs with and without detected metastases with respect to drug treatment ($P = .29$). The survival times of the 4 dogs treated with mitotane that had metastatic disease were 43, 61, 62, and 172 days. The survival times of the 3 dogs that were treated with trilostane were 4, 50, and 292 days. The 1 dog with metastatic disease, which was treated with both drugs, survived 159 days. No statistical analysis was attempted on these data.

The 1-year survival fraction for dogs with metastatic disease was 0% regardless of the drug treatment regimen. In dogs with metastatic disease treated with mitotane, the median survival time was 61 days (lower 95% CI, 43 days; upper 95% CI, not calculated) and for trilostane also was 61 days (95% CI, 4–172 days). The 1-year survival fraction for dogs without metastatic disease was 33.3% (95% CI, 7.8–62.3%) if they were treated with mitotane and 50.0% (95% CI, 29.9–67.2%) if treated with trilostane. Both drug treatments had lower survival fractions at 2 years (mitotane, 22.2%; 95% CI, 3.4–51.3% and trilostane, 23.1%; 95% CI, 9.4–40.3%). In dogs without metastatic disease treated with mitotane, the median survival time was 195 days (95% CI, 33–952 days) and for trilostane was 353 days (95% CI, 163–531 days).

Cox Proportional Hazards Model. In the final multivariable Cox proportional hazards model the presence of metastatic disease (HR 5.3; 95% CI, 2.06–13.5; $P = .001$) was significantly associated with an increased hazard of death. There were no other predictor variables that were significant at either the level of the univariable or multivariable model. Specifically, there was no significant effect of drug treatment (mitotane compared with trilostane or both drug treatments) on survival rates. This remained true when the dogs treated with both mitotane and trilostane (n = 2) were subsequently excluded from the analyses. The lack of a significant finding for drug treatment was likely because of the small number of observations in this study (total n = 37) and thus a lack of power to detect small effects (HR < 5).

The confounding effects of drug treatment and veterinary center were assessed in the final model. Neither variable was significant or had an important effect on the HRs associated with the presence of metastatic disease. Interaction terms were explored, but were not included in the final model because of the small number of observations in the study. The final model did not violate the proportional hazards assumption (based on Schoenfield's residuals). The model was checked for outliers and influential points. Two dogs were identified as influential and the model was rerun without these observations. However, omission of these observations had no significant effect on the final model.

Discussion

This study evaluated factors that may influence survival in dogs treated for ADH with either mitotane or trilostane. There was a significant difference in survival between animals with metastatic disease at the time of diagnosis and those without, but no significant difference in survival between dogs treated with mitotane or trilostane. The fact that the study was able to detect a significant difference between dogs with and without metastatic disease demonstrates that the study was sufficiently well powered to detect large differences. Therefore if there were, in fact, a difference between mitotane and trilostane, then it was a small effect, which this study could not detect. This study provides important information for clinicians who are presented with dogs with ADH, because, until now, there may have been a presumption that by an adrenocorticolytic treatment (such as mitotane) would be superior. The results of the present study do not support this view.

Complete removal of a functional adrenal tumor causing HAC offers a good prognosis if dogs survive the immediate postoperative period. In 1 study, the median survival time after surgical removal was just <2 years, although some dogs survived for >4 years.[23] However, animals with untreated ADH are difficult surgical candidates because of the increased anesthetic risk (because of poor respiratory and hepatic function), hypercoagulability (leading to an increased risk of pulmonary thromboembolism), poor vascular tone (leading to poor hemostasis), delayed primary wound healing, and difficulty in surgical exposure. Acute postoperative hypoadrenocorticism because of pre-existing contralateral adrenal atrophy and postoperative pancreatitis and peritonitis, as well as ischemic necrosis and multiple

organ failure, are described.[23–26] Postoperative intensive care facilities therefore are essential. Even in referral centers, perioperative mortality rates are in the range of 19–60%.[23–26] The costs of surgical management may be considerable in the short term. For all of these reasons, surgery can be considered a "high gain but high risk" strategy and therefore many owners opt for medical treatment rather than surgical intervention.

In our study population, it is presumed that the dogs had factors that prevented surgery as a viable option, such as gross metastases at the time of diagnosis, local invasiveness, and financial or owner issues. Because of the retrospective nature of this study, it was unclear in some cases why medical management was selected, and there could be concern that surgery was precluded because of advanced disease. However, because very few animals in the study had evidence of metastases or blood vessel invasion, concern about advanced disease was not an important factor.

Having decided to treat a case medically, the criteria used by clinicians to select a particular drug treatment were not clear because of the retrospective nature of this study. The choice of drug treatment may have been influenced by practical factors such as cost, availability (a Special Treatment Authorization is required to obtain mitotane in the United Kingdom), and individual clinician or center preference. The last two of these likely were major factors in the selection criteria. In the early study period, trilostane was not readily available in the United Kingdom, and therefore from the years 1996–1998 all dogs were treated with mitotane. Between 1998 and 2001 both products were available. From 2002 onward, 14/16 dogs were treated with trilostane (as this was the UK veterinary-licensed product from 2005). It is therefore likely that clinician choice was influenced by drug availability. It is known that dogs in both the mitotane and trilostane groups were from the same general population of dogs affected with ADH as evidenced by the lack of significant differences between any of the population variables measured (Table 4). Crucially, there were no detectable differences in the numbers of dogs with signs of overt malignancy (blood vessel invasion or presence of metastatic disease) that were prescribed either mitotane or trilostane.

Two protocols for the treatment of PDH with mitotane are described,[12] one utilizes selective adrenocorticolysis and includes an induction period of daily doses of mitotane followed by a weekly maintenance dose (as in this study),[2] the second is a high-dose nonselective protocol designed to completely destroy the adrenal cortices, followed by daily and lifelong corticosteroid and mineralocorticoid supplementation.[26,27] There have been no studies examining the use of a nonselective protocol in the treatment of ADH. In PDH, the selective destruction of the adrenal cortices with mitotane is considered to be safer for the patient, because the zona glomerulosa and mineralocorticoid production are preserved. Therefore a "selective protocol" was chosen for the ADH cases in this study because it decreased the risks of adverse effects (including hypoadrenocorticism) and because this protocol is the only one that has been reported in ADH cases.[12,27]

Most dogs described here received the current recommended trilostane dosage for PDH of 2.2–6.7 mg/kg from the manufacturer's data sheet. Two small breed dogs in this study (weights, 3.2 and 5 kg) received trilostane but at a time when the 30 mg capsule was the smallest formulation available, hence their doses were 9.3 and 6 mg/kg, respectively. However, at the time of presentation, the recommended trilostane dosage was higher than is currently used and hence these dogs still fell within manufacturer guidelines of 2–12 mg/kg.

Although some authors suggest that mitotane dosage should be increased when treating dogs with ADH,[28] this study does not support increased trilostane dosage over that used to manage PDH, but work in this area is ongoing.

A change in trilostane treatment usage has occurred over the study period. Current literature reflects the fact that performing ACTH stimulation tests for monitoring response to treatment (ie, at 4–6 hours postmedication), starting dosage, and therapeutic targets for trilostane still are under review for patients with ADH.[10]

This study was possible because for a period of time UK centers were using both trilostane and mitotane for medical management of HAC. The retrospective study design was chosen to encompass the period of time when both trilostane and mitotane were available as medical treatment for HAC. Because of the cascade system of veterinary prescribing in Europe, trilostane now is the authorized product and therefore is considered to be the first choice for the treatment of PDH. A prospective study would therefore be difficult to complete. In addition, because the treatment protocols are so different, it would be difficult to design a blinded trial. Furthermore, a multicenter approach over a number of years was deemed necessary because of the rarity of this disease. However, with this design there is always a risk that selection bias may be introduced as a result of differences among study populations from different veterinary centers. In this study, there was variation among centers regarding the choice of drug treatment. However, as there was no geographical variation found when age at diagnosis, weight at diagnosis, and reproductive status were compared, it was concluded that the dogs from each center were derived from populations that were not substantially different and could therefore be combined for further analysis. Comparisons among centers and treatment groups in terms of breed were not possible because of the small numbers of animals in some of the breed categories.

Because there are no published reports describing survival of dogs with HAC that did not undergo any form of treatment, it is impossible to compare with historical "no treatment" controls. In addition, direct comparison of survival times from this study with historical groups of surgically managed dogs is not recommended because it cannot be guaranteed that the dogs are from the same population, meaning selection bias may be introduced. Prospective randomized studies comparing surgery to medical management may be difficult given the financial differences and difference in short-term risk.

One limitation of this study (and of other similar studies) is that the histological subtype of the adrenal tumor was not established in most cases. Percutaneous antemortem adrenal biopsies are a high-risk procedure and as such are not routinely obtained. The histological tumor type is likely to have a substantial effect on survival.[29] Given that approximately half of dogs with ADH will have a malignant adrenal tumor,[13] it is likely that a proportion of the dogs in this study had malignant neoplasia. If this is true, then there may have been an adverse affect on survival. However, because of the retrospective nature of this study, it was not possible to evaluate this variable.

Another potential limitation of this study was that the date of institution of medical treatment was taken as the start date for survival analysis because it is a clearly defined point in time. Only 1 dog in the current study had a prolonged period of time between diagnosis and treatment (174 days). This dog had pancreatitis and pyelonephritis at the time of diagnosis of ADH (confirmed by LDDST, ACTH concentration of <5.0 ng/mL, and a large unilateral adrenal mass on abdominal ultrasonography) and therefore was medically managed for these conditions before initiating mitotane treatment. Despite this, if the date of diagnosis of all patients is used for analysis, the same pattern of significance is seen in all variables evaluated in this study.

Dogs in this study tended to be middle- to older-aged and of medium to large body size, which is in agreement with previous studies.[13,30] Forty-six percent of dogs in the study were >20 kg.[30] Similar to other investigations, one-third of the dogs in this study were Labrador Retrievers or Labrador Retriever cross breeds.[30] However, it is unclear if this represents a true increased prevalence in this breed or is related to breed popularity bias within the United Kingdom.

Almost one-third of dogs (11/37) in this study had concurrent disease during follow-up, and it is likely in some cases that concurrent disease had an impact on survival. In 9 dogs, death or the decision to perform euthanasia was thought to be because of signs of another disease unlikely related to the ADH (eg, spinal disease, cardiac disease, mammary neoplasia). A previously published study found that the majority of animals with PDH did not die because of diseases associated with PDH or its treatment but rather failure of other organs (eg, heart, liver, kidneys), unrelated neoplasia, or geriatric diseases (eg, gradual deterioration, incontinence).[2] The frequency of concurrent disease could be viewed as a limitation of this study, but because of the study population (median age, 11 years) some form of concurrent disease in a proportion of the dogs is to be expected. In addition, the quality of life of the animals or the efficacies of the treatments were not assessed in this retrospective study in either treatment group.

The number of dogs enrolled in this study is comparable to similar studies on ADH in the veterinary literature.[13,23–25,29] This study includes the use of trilostane treatment in 22 dogs with ADH and is therefore the largest case series of its kind currently published. Despite this, the study was underpowered to detect small effects. The small study size likely reflects the rarity of adrenal-dependent as opposed to pituitary-dependent disease. As such, future studies will require further collaborations among large numbers of veterinary centers to ensure enrollment of sufficient numbers of ADH dogs to detect small differences.

In conclusion, medical management is a reasonable treatment option for ADH dogs. It is unlikely that the choice of treatment (mitotane or trilostane) has a major effect on survival times in dogs medically managed for ADH. The presence of metastatic disease adversely affects outcome. Additional large clinical studies are required to support these findings and allow for clear treatment recommendations.

Footnotes

[a] Lysodren, Bristol-Myers, Montreal, Quebec, Canada
[b] Vetoryl, Dechra Pharmaceuticals, Shrewsbury, Shropshire, UK
[c] Synacthen, Alliance Pharmaceuticals, Chippenham, UK
[d] Dexadreson, Intervet UK Ltd, Milton Keynes, UK
[e] ACTH IRMA; Nichols Institute, Cambridge Specialist Laboratories, Cambridge, UK
[f] Stata Statistical Software: Release 10.1, 2005, StataCorp, College Station, TX

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