Outcomes of the addition of pasireotide to traditional adrenal-directed treatment for dogs with pituitary-dependent hyperadrenocorticism secondary to macroadenoma: 9 cases (2013–2015)

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OBJECTIVE
To evaluate clinical signs, endocrine test results, and pituitary tumor size for dogs with medically managed pituitary-dependent hyperadrenocorticism (PDH) and macroadenoma following 6 months of concurrent treatment with pasireotide.

DESIGN
Prospective case series.

ANIMALS
9 client-owned dogs with PDH and macroadenoma in which PDH had been successfully managed with adrenal-directed treatment (trilostane or mitotane).

PROCEDURES
Dogs were given pasireotide (0.03 mg/kg [0.014 mg/lb], SC, q 12 h) for 6 months, while adrenal-directed treatment was continued. Physical examination, basic clinicopathologic testing, ACTH stimulation testing, and plasma ACTH concentration measurement were performed before (baseline) and 3 and 6 months after treatment began. Measurements of pituitary gland volume and pituitary gland-to-brain ratio were performed via MRI at baseline and 6 months after treatment began.

RESULTS
No dog developed neurologic abnormalities or signs of adverse effects during the study period. No differences from baseline were identified in clinicopathologic values, ACTH stimulation test results, or plasma ACTH concentration at the 3- or 6-month assessment points. After 6 months of pasireotide treatment, 6 dogs had decreases in MRI-measured values, and 3 had increases.

CONCLUSIONS AND CLINICAL RELEVANCE
Pasireotide as administered in this study had no noted adverse effects on dogs with PDH and macroadenoma successfully managed with standard treatment. Placebo-controlled, randomized studies are needed to determine whether pasireotide protects from the development of neurologic signs or improves outcome in dogs with pituitary macroadenomas. (J Am Vet Med Assoc 2018;252:1403–1408)

Functional ACTH-secreting pituitary adenomas (Cushing disease or PDH) secrete inappropriate amounts of ACTH, which results in disorderly and excessive production of cortisol by the adrenal glands. In dogs, such pituitary adenomas have a reported incidence of 0.2%/y (1 to 2 cases/1,000 dogs/y), with approximately 100,000 dogs affected yearly. Pituitary-dependent hyperadrenocorticism accounts for approximately 85% to 90% of cases of Cushing syndrome (hypercortisolism from any source) in dogs, with the remainder of cases being the result of functional adrenal tumors, aberrant expression of gastric inhibitory polypeptide receptors (meal or food induced), or occult or atypical disease.

Two theories (hypothalamic and pituitary) have been proposed to explain the development of ACTH-producing pituitary tumors (corticotrophinomas). The hypothalamic theory posits that the hypothalamus stimulates corticotrophs through enhanced secretion of corticotropin-releasing hormone and vasopressin. Concurrent defects in pituitary glucocorticoid receptors lead to greater stimulation of the corticotroph cells as a result of a lower inhibitory action of cortisol on corticotropin-releasing hormone and ACTH synthesis. A mutation in the glucocorticoid receptor gene results in a reduction in the number of DNA-binding sites while maintaining an affinity for cortisol. This de novo mutation promotes a general resistance to glucocorticoids that precedes the formation of the corticotrophinoma. Studies involving

ABBREVIATIONS
HPA Hypothalamic-pituitary-adrenal
P:B Pituitary gland-to-brain
PDH Pituitary-dependent hyperadrenocorticism
SST Somatostatin

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healthy dogs treated with trilostane to decrease cortisol secretion have shown that the resulting decrease in negative feedback to the HPA axis results in pituitary gland enlargement. Reported findings for canine ACTH tumor cells reinforce that such events would first lead to corticotroph hyperplasia followed by a subsequent somatic mutation in the proteins that control the cell cycle leading to tumor development.\(^5\)

Other potential evidence supporting the hypothalamic theory of PDH includes dopaminergic neurodegeneration in elderly subjects\(^11\)–\(^13\) or low expression of subtype 2 dopamine receptors by corticotroph cells, which results in less dopaminergic inhibition and subsequent hyperplasia of pituitary corticotrophs.\(^14\)–\(^16\) The principal evidence opposing the hypothalamic theory is the presence of tumor clonality in most human adenomas, suggesting a primary pituitary origin.\(^17\)\(^,\)\(^18\)

We are only just beginning to investigate genes and protein expression associated with PDH in dogs. The demonstration of expression of SST-receptor subtypes (primarily SST2 with low amounts of SST5, the opposite of findings in humans) and subtype 2 dopamine receptors in corticotroph adenomas in dogs offers the possibility for novel medical treatment of PDH with SST analogs and dopamine agonists.\(^15\)

Pasireotide (also known as SOM230) is an SST-receptor ligand with high binding affinity for multiple receptor isoforms (SST1, SST2, SST3, and SST5). The SST5 and SST2 isoforms are highly expressed in ACTH-secreting pituitary adenomas; SST5 is most commonly overexpressed in humans, whereas SST2 appears to be most common in dogs.\(^15\) Pasireotide has been approved by the US FDA for the treatment of humans with hyperadrenocorticism for whom pituitary surgery is no option or has not been curative.\(^19\)

Pasireotide has been evaluated in dogs with PDH at a dose of 0.03 mg/kg (0.014 mg/lb), SC, every 12 hours for 6 months. In that study,\(^20\) a significant decrease was identified in plasma ACTH concentration, urinary cortisol-to-creatinine concentration ratio, and adenoma size (assessed via MRI), along with an improvement in clinical signs, without adverse effects. However, tumor volume and tumor size (as assessed via P:B ratio) were not evaluated. The most accepted definition of pituitary macroadenoma in dogs is a tumor that is > 1 cm in diameter, extends above the sella turcica, or has a P:B ratio > 0.31.\(^21\)

The 2 main treatments for dogs and cats with hyperadrenocorticism are trilostane, which is an inhibitor of \(3\ \beta\)-hydroxysteroid dehydrogenase, and mitotane (o,p\(^\prime\)-DDD), which is an adrenolytic agent.\(^22\) Pasireotide, trilostane, and mitotane reduce the amount of cortisol in circulation through distinct mechanisms of action at different levels of the HPA axis. Pasireotide inhibits ACTH secretion from the pituitary gland, whereas trilostane and mitotane inhibit the biosynthesis of cortisol in the adrenal cortex. It has been hypothesized that the combined effect of these 2 categories of medications may be superior to each category alone in patients with hyperadrenocorticism, thereby providing a scientific rationale for investigating the effects of combined treatment with the 2 categories of agents.

The purpose of the study reported here was to evaluate the effects of pasireotide on endocrine function (plasma ACTH concentration and serum cortisol concentrations during ACTH stimulation testing) and pituitary tumor size and volume in dogs with hyperadrenocorticism secondary to pituitary macroadenoma, for which clinical signs had been well controlled with traditional adrenal-directed treatment (trilostane or mitotane). An additional aim was to evaluate the safety of the combined treatments.

**Materials and Methods**

**Ethics statements**

The study protocol was approved by the Institutional Animal Care and Use Committee of the VCA West Los Angeles Animal Hospital following National Institutes of Health guidelines. All owners signed a consent form to allow the administration of the tested drug (pasireotide) and the performance of laboratory tests and MRI scans.

**Animals and screening**

From January 1, 2013, through January 1, 2015, dogs were considered for enrollment if they had been evaluated at a specialty veterinary hospital\(^b\) for the possibility of transsphenoidal hypophysectomy for PDH.\(^3\) The diagnosis of PDH had been previously confirmed on the basis of characteristic clinical signs and results of a complete physical examination, hematology and serum biochemical analyses, and urinalysis. Previous endocrine testing included measurements of basal plasma ACTH concentration and urinary cortisol-to-creatinine concentration ratio (first morning urine sample obtained at home by the owner) as well as low-dose dexamethasone suppression testing or ACTH stimulation testing. Hypercortisolism was diagnosed on the basis of failure of cortisol suppression to a serum concentration < 1.4 µg/dL by 8 hours following low-dose dexamethasone administration, a urinary cortisol-to-creatinine concentration ratio > 13 X 10\(^6\), or a post-ACTH stimulation serum cortisol concentration > 22 µg/dL.\(^22\) All dogs initially identified as hypercortisolemic on the basis of urinary cortisol-to-creatinine concentration ratio had a low-dose dexamethasone suppression or ACTH stimulation test result to corroborate the diagnosis.

After the diagnosis of hypercortisolism, PDH was confirmed by measurement of plasma ACTH or serum cortisol concentration; ACTH concentrations > 40 pg/mL or > 50% suppression of serum cortisol concentration during low-dose dexamethasone suppression testing was considered diagnostic of PDH. All assays were performed at a commercial clinical veterinary laboratory\(^b\) and had been previously validated. All dogs were deemed clinically well controlled on the basis of owner and veterinarian (DSB)
Magnetic resonance images of the brain were acquired with a 1.5-T closed-bore MRI machine by use of a modified protocol to confirm the presence of a pituitary macroadenoma, with dogs anesthetized and positioned in sternal recumbency. T1-weighted images were acquired in axial, coronal, and sagittal planes before and after administration of gadoversetamide (0.3 mL/kg [0.14 mL/lb], IV). Optimal image quality was obtained with the following settings: repetition time, 500 to 600 milliseconds; echo time, 10 to 14 milliseconds; slice thickness, 1 mm; slice spacing, 0.2 mm; field of view, 256 X 192 pixels; and display magnification, 2.4X. T2-weighted non–contrast-enhanced images were acquired with a repetition time of 5,000 milliseconds, echo time of 86 milliseconds, and similar slice thickness, field of view, and magnification.

**Participants**

Following completion of the diagnostic evaluation, 9 dog owners elected not to proceed with transsphenoidal hypophysectomy and provided consent to enroll their dog in the study. Inclusion criteria were a diagnosis of PDH, control of clinical signs of PDH with medical treatment, evidence of a macroadenoma on MRI, and absence of neurologic disease as well as the owners’ ability and willingness to adhere to the requirements of the study. Pituitary macroadenoma was defined as a tumor > 1 cm in diameter with extension above the sella turcica, a P:B ratio > 0.31, or both. The P:B ratio was calculated as the height of the pituitary gland (mm) divided by the area of the brain (cm²). Exclusion criteria were nonadrenergic disease (eg, diabetes mellitus, systemic infection, chronic gastrointestinal disease, or cardiac disease) and receipt of medications associated with polyuria and polydipsia or known to affect the HPA axis.

All 9 dogs met these criteria. Given that they had all had been clinically well controlled on their existing medical treatment, all were maintained on their existing treatment dosages throughout the 6-month study to prevent the recurrence of clinical signs of PDH and adverse events if the medications were withdrawn and pasireotide was ineffective in controlling clinical signs independent of an effect on tumor volume or size.

**Study protocol**

Baseline data were obtained regarding dog signalment, duration of clinical signs prior to enrollment, current medical treatments, initial endocrine and clinicopathologic test results, and initial MRI data. Owners were provided with pasireotide free of charge and instructed to administer the drug at a dosage of 0.03 mg/kg, SC, every 12 hours for 6 months. Clinical signs evaluation, physical examination, biochemical evaluation (CBC, serum biochemical analysis, and urinalysis), and endocrine testing (ACTH stimulation testing and plasma ACTH concentration measurement) were performed 3 and 6 months after study treatment began. Magnetic resonance imaging of the brain was performed at enrollment and again 6 months after treatment began.

**Statistical analysis**

Plasma ACTH concentration, pituitary volume, P:B ratio, and pre- and post-ACTH stimulation serum cortisol concentrations were compared between baseline (0 months) and 6-month measurements and between 3- and 6-month measurements by means of the 2-tailed paired t test. Repeated-measures ANOVA was performed to compare plasma ACTH concentrations at 0, 3, and 6 months. Values of $P < 0.05$ were considered significant for all analyses.

**Results**

**Animals**

The 9 dogs with PDH and macroadenomas included 6 females (all neutered) and 3 males (2 neutered and 1 sexually intact), which ranged in age from 7 to 12 years and weighed between 12.5 and 43.6 kg (27.5 to 95.9 lb). There were 5 mixed-breed dogs, 2 Labrador Retrievers, 1 Poodle, and 1 Golden Retriever. Each was being concurrently treated with trilostane (n = 8) or mitotane (1) and had been treated for 6 to 22 months prior to enrollment (Supplementary Table S1, available at avmajournals.avma.org/doi/suppl/10.2460/javma.252.11.1403).

Throughout the 6 months of pasireotide treatment, clinical signs of PDH remained well controlled as determined via owner assessment, physical examination (DSB), routine laboratory evaluation (data not shown), and ACTH stimulation testing (Supplementary Table S2, available at avmajournals.avma.org/doi/suppl/10.2460/javma.252.11.1403). No significant changes in CBC, serum biochemical, or urinalysis data were identified over the study period, nor were any neurologic abnormalities or adverse drug events (development of gastrointestinal signs or diabetes mellitus) noted for any dog.

**Clinical findings**

No significant differences in mean ± SD plasma ACTH concentrations were identified between baseline (before treatment; 123 ± 74.6 pg/mL) and 3-month (122 ± 57.6 pg/mL) and 6-month (125.4 ± 55.6 pg/mL) measurements ($P ≥ 0.62$) or among measurements overall ($P = 0.99$; Supplementary Table S2). Over the 6-month period, 2 dogs had a decrease in ACTH concentration (1 with a pituitary tumor that progressed in size and 1 with a pituitary tumor that decreased in size), 3 dogs had no change in ACTH concentration (1 with a pituitary tumor that progressed in size and 2 with a pituitary tumor that decreased in size), and 4 dogs had an increase in ACTH concentration (1 with a pituitary tumor that progressed in size and 3 with a pituitary tumor that decreased in size). No significant ($P ≥ 0.11$) differences in pre- or post-ACTH stimulation serum cortisol concentrations were identified between baseline and 3- or 6-month measurements.
Tumor volume and P:B ratio

No significant ($P = 0.94$) change in the P:B ratio was detected between baseline measurements (0.96 ± 0.45) and 6-month measurements (0.94 ± 0.40; Supplementary Table S3, available at avmajournals.avma.org/doi/suppl/10.2460/javma.252.11.1403). Pituitary tumor volume also did not differ significantly ($P = 0.08$) between baseline measurements (1,862 ± 1,689.5 mm$^3$) and 6-month measurements (1,690.6 ± 1,400 mm$^3$). Over the 6-month period, pituitary tumor volume and P:B ratio increased in 3 dogs and decreased in 6 dogs. The direction of change in tumor volume and P:B ratio was the same for each dog. Magnitude of changes in plasma ACTH concentration and tumor volume varied among dogs (Supplementary Table S4, available at avmajournals.avma.org/doi/suppl/10.2460/javma.252.11.1403).

Discussion

In the study reported here, addition of pasireotide to traditional medical treatment with trilostane or mitotane for dogs with PDH and macroadenomas resulted in a decrease in pituitary tumor volume in two-thirds (6/9) of dogs, whereas one-third (3/9) had an increase in tumor size. This variability among patients likely reflected the large range in tumor sizes at the start of the study, and tumors that failed to have a reduction in size may have lacked SST receptors. Reduction in pituitary tumor size has been reported in human patients with PDH treated with pasireotide for 1 year.25 Interestingly, none of the dogs, even those in which the tumor enlarged, developed neurologic abnormalities during the 6-month treatment period. The observed decrease in tumor volume without a reduction in the P:B ratio likely reflected the limitations of 2-D measurement in the assessment of overall tumor size.

In a previous study26 of survival time, neurologic response, and prognostic factors for dogs with pituitary masses treated with or without radiation therapy, the P:B height ratio and the P:B area ratio were evaluated. Significant differences were identified between dogs with and without neurologic signs regarding tumor height and these 2 ratios. In addition, both ratios were significantly associated with survival time.26 A different study9 showed that the P:B ratio has prognostic value with regard to surgical outcome in dogs with PDH treated by transphenoidal hypophysectomy.

Pasireotide treatment in combination with ongoing adrenal-directed treatment yielded no clinically important adverse effects such as gastrointestinal signs or diabetes mellitus in the dogs of the present study. In healthy human volunteers, pasireotide treatment may result in hyperglycemia owing to inhibition of incretin secretion. Other than hyperglycemia, pasireotide treatment of humans with hyperadrenocorticism has also been associated with gastrointestinal adverse effects.27-28 The lack of grossly observed adverse effects in the dogs included in the present study may have been related to dose-dependent effects or differences between dogs and humans in the distribution of SST receptors. At the dosage and duration used in the present study and a previous study,29 pasireotide appeared to be safe for adult dogs, although additional studies would be needed to confirm this supposition.

In the previous study29 of pasireotide treatment involving 20 dogs with PDH,20 patients had a significant decrease in tumor size, as assessed by maximal tumor height measured via MRI. However, no tumor volume measurements were reported, nor was the P:B ratio reported, which might have allowed for a more thorough evaluation of tumor response. Two (10%) dogs in that study20 fulfilled the criteria for macroadenoma (> 1 cm in height); however, no decreases in pituitary tumor size were identified in any dog with initial tumor height exceeding 7 mm. In contrast, all 9 dogs in the present study fulfilled the criteria for macroadenoma, and two-thirds had a decrease in tumor size. The difference in tumor response between the 2 studies may have been related to the tumor size, low numbers of patients, or coadministration of adrenal-directed treatment in the present study but not the other study.

No important changes in plasma ACTH concentration were observed in any dog of the present study. This apparent lack of an effect of pasireotide on this variable in our study versus the other study20 may have reflected the coadministration of adrenal-directed treatment, which would have resulted in a decrease in cortisol secretion, loss of negative feedback to the HPA axis, and subsequent increase in ACTH secretion. We elected not to discontinue adrenal-directed treatment for dogs enrolled in the present study because this treatment was well tolerated and the clinical signs of PDH were controlled. Additionally, a goal of the study was to assess the effect of pasireotide on pituitary tumor growth in patients with reduced negative feedback to the HPA axis as a result of an adrenolytic or adrenal enzyme blocker.

No consistent parallel effects of pasireotide on plasma ACTH concentrations and changes in tumor size were identified in the study reported here, except in 2 dogs in which ACTH concentrations and tumor volumes changed in a similar direction (Supplementary Table S4). Reductions in pituitary weight have been reported for healthy rats treated with pasireotide alone or in combination with osilodrostat (11ß-hydroxylase inhibitor).29 These observed effects in rats are consistent with the inhibitory effects of SST on pituitary gland hormone secretion50 and were expected given the well-characterized effect of SST analogs on pituitary adenoma volume reduction in humans.28,31 The lack of similar effects in a large proportion (7/9) of dogs with pituitary macroadenomas in the present study may have reflected differences in SST receptor distributions, the differential effects of SSTs on tumor growth versus hormonal secretion, or the coadministration of adrenal-directed treatment.

In 1958, the first report32 was published of pituitary macroadenoma and high plasma ACTH concentration in a human patient treated by total bilateral
adrenalectomy for hyperadrenocorticism. Similar cases were subsequently reported, and these observations provided new clues regarding the pathogenesis of this condition. They also raised concern that adrenalectomy could induce or trigger the growth of a pituitary macroadenoma, with a risk of subsequent complications related to pituitary tumor burden. Nelson syndrome is generally defined as the association of an expanding pituitary tumor and a high plasma ACTH concentration after adrenalectomy in humans with hyperadrenocorticism. The prevalence of Nelson syndrome in humans ranges from 8% to 29%, and the interval between adrenalectomy and diagnosis of this condition ranges between 0.5 and 24 years.35

Although bilateral adrenalectomy is uncommonly performed to treat PDH in dogs, adrenal-directed medications used in the management of PDH may also contribute to the development of a pituitary macroadenoma and physiologic effects similar to the human Nelson syndrome via loss of negative feedback. In a previous study,3 10 of 26 dogs referred for transsphenoidal hypophysectomy secondary to a macroadenoma had been treated for PDH (9 with trilostane and 1 with mitotane) for 8 to 24 months before surgery. No pretreatment MRI examination was performed, but the high prevalence (38%) of macroadenomas in that group is notable. In an earlier study,34 the MRI appearance of the pituitary gland in dogs with PDH treated with the adrenolytic agent mitotane was evaluated. Over a 12-month period, tumor size increased in 6 of 13 dogs, and no dog had a decrease in tumor size. In addition, 2 of the 13 dogs developed CNS signs as a result of tumor growth. In the present study, the 1 dog that received mitotane had a reduction in tumor size with the combined treatment, and we therefore suggest that the concurrent use of pasireotide in patients treated with mitotane may attenuate tumor growth.

Prospective studies on the prevalence of expanding pituitary tumors and high plasma ACTH concentrations in dogs undergoing treatment with adrenal-directed treatment are lacking, likely because of the need for serial MRI examinations. The effect of reduced negative feedback through the inhibition of cortisol secretion by daily trilostane administration on the HPA axis has been investigated in clinically normal dogs. In that study,9 dogs were given trilostane at 5 mg/kg (2.3 mg/lb) twice a day every day for 8 weeks (n = 8) or 16 weeks (3). After trilostane treatment began, plasma ACTH concentration increased remarkably, and the pituitary gland became enlarged as assessed via MRI. After treatment concluded, histologic examination of pituitary gland specimens revealed greater cytoplasmic areas of the pituitary corticotrophs and a greater ratio of pituitary corticotrophs to all cells in the anterior pituitary lobe in trilostane-treated dogs versus untreated control dogs. In addition, histologic examination revealed bilateral adrenal cortical hyperplasia. Results of real-time PCR assay in the same study9 indicated that pituitary gland expression of proopiomelanocortin and adrenerginal gland expression of ACTH receptors was greater in the trilostane-treated dogs as well. These findings suggest that reduced negative feedback induced proliferation of the pituitary corticotrophs and pituitary gland enlargement in healthy dogs. They also suggest that the inhibition of cortisol secretion induced by trilostane may increase the risk of corticotroph adenoma growth acceleration in dogs with hyperadrenocorticism, resulting in a Nelson syndrome–like state.

Concurrent use of pasireotide in dogs being treated with trilostane may prevent the progression of pituitary tumors and the development of this state. It is important to note that although it is highly plausible that a condition similar to human Nelson syndrome exists in veterinary medicine (given the similarities between dogs and humans in other PDH characteristics), no study35 has definitively shown an association between tumor growth rate and adrenal-directed medical treatment in dogs, and additional research is needed in this regard.

Limitations of the study reported here included a small sample size and lack of a placebo-treated control group of similar dogs, which precluded drawing any conclusions regarding the effectiveness of the pasireotide treatment. Maintenance of previously administered adrenal-directed medical treatment throughout the study period may also have interfered with assessment of the suppressive effects of pasireotide on ACTH secretion, given that such medications are known to increase ACTH secretion by corticotrophs secondary to a loss of negative feedback to the HPA axis. The justification for continuing adrenal-directed treatment was that we believed it would have been unethical to withhold medications that had been effective and safe in controlling the clinical signs of PDH. Finally, because no histologic examination of pituitary gland specimens was performed, it remains unknown whether the included dogs had pituitary adenoma or carcinoma.

Although additional research is needed to determine the effectiveness of pasireotide for protecting against the progression of macroadenomas and associated neurologic signs in dogs successfully managed for PDH and macroadrenoma with trilostane or mitotane, no neurologic signs or grossly apparent adverse effects were observed during pasireotide treatment, suggesting such treatment was safe in those dogs as administered. Placebo-controlled, randomized trials involving a larger group of patients are needed to investigate the efficacy of combined adrenal- and pituitary-directed treatment in preventing the progression of macroadenomas and improving overall outcome. Future trials should involve evaluation of such treatment combinations in the initial treatment of dogs with PDH, as an adjunct treatment approach for patients with residual tumor volume following transsphenoidal hypophysectomy or radiation therapy, or in dogs that develop macroadenomas following adrenalectomy (rarely performed in veterinary medicine) or traditional adrenal-directed treatment.
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Footnotes

a. VCA West Los Angeles Animal Hospital, Los Angeles, Calif.
b. Antech Diagnostics Laboratory, Irvine, Calif.
c. Closed-bore MRI machine (1.0 T), GE Healthcare, Waukesha, Wis.
d. Optimark, Mallinckrodt Pharmaceuticals, Hazelwood, Mo.
e. Novartis Pharma AG, Basel, Switzerland.

References