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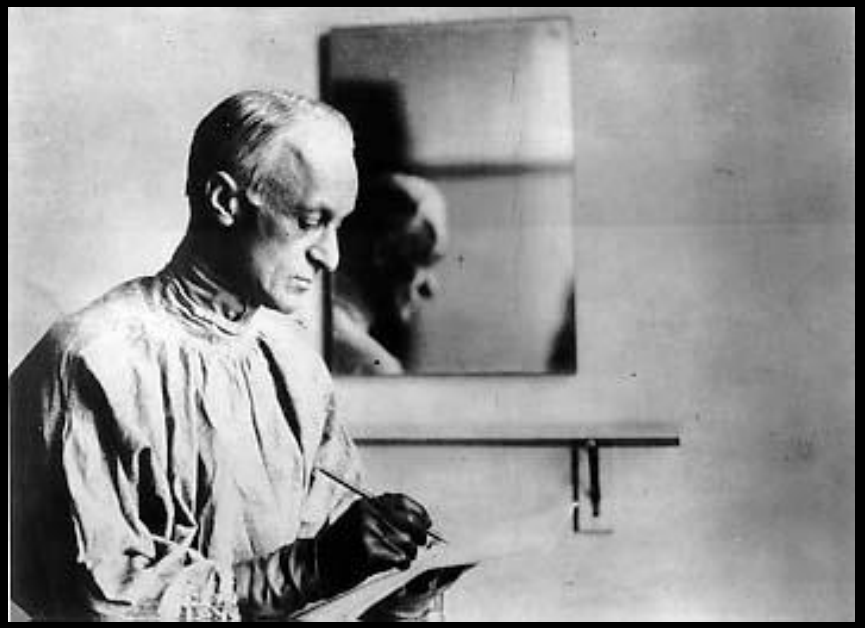
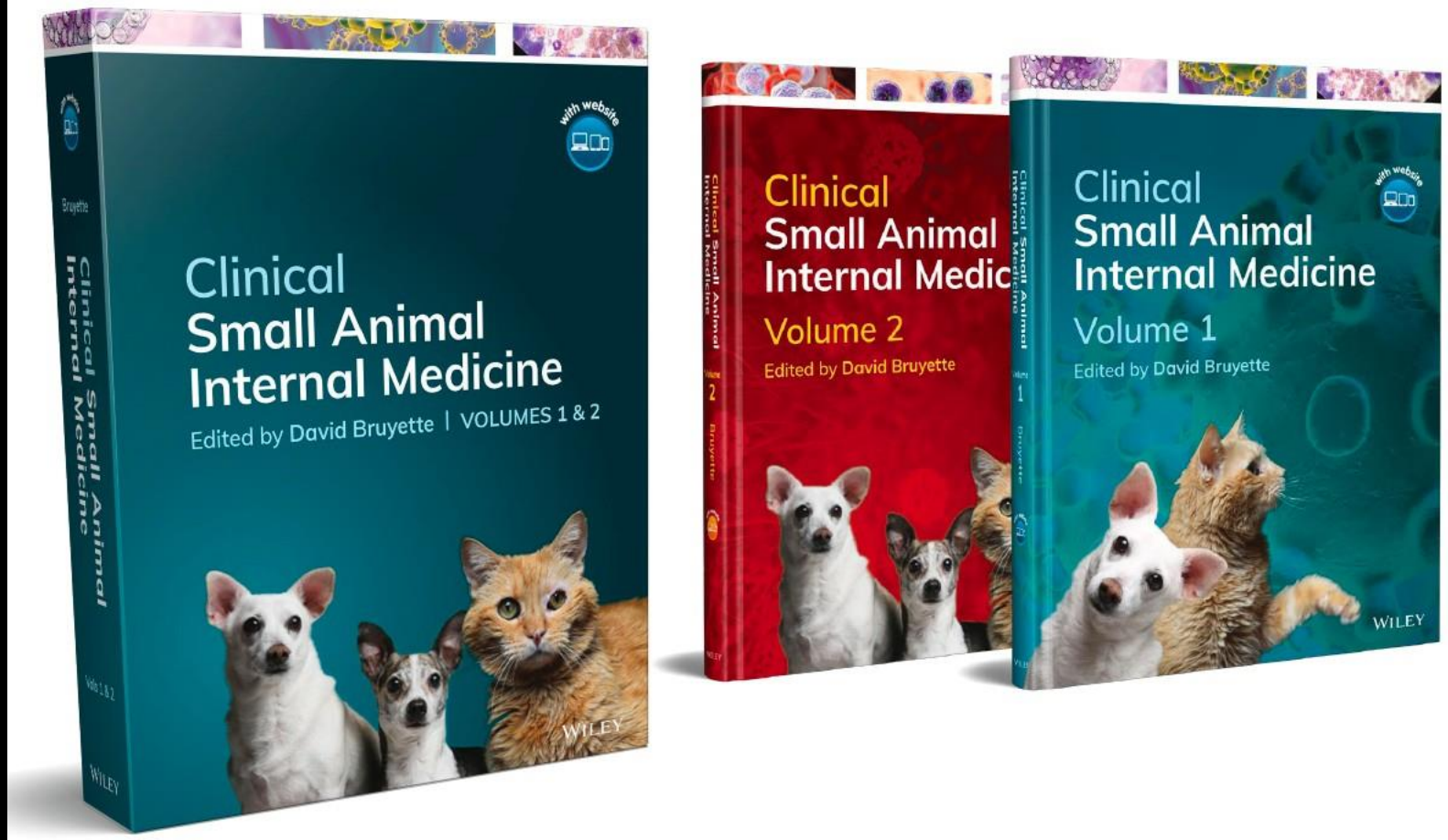
Canine Hyperadrenocorticism

Pathogenesis and Diagnostic Approach

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The Secret Sits

We dance round in a ring and suppose,
But the Secret sits in the middle and knows.

Robert Frost

Original Article

Histopathologic Findings in Canine Pituitary Glands

Veterinary Pathology
1–9

DOI: 10.1177/0300985818786211
journals.sagepub.com/home/vet

Margaret A. Miller[1,2], David S. Bruyette[3], J. Catharine Scott-Moncrieff[4], Tina Jo Owen[5], José A. Ramos-Vara[1,2], Hsin-Yi Weng[2], Andrea L. Vanderpool[1,2], Annie V. Chen[5], Linda G. Martin[5], Deidre M. DuSold[1], and Sina Jahan[6]

Abstract

To optimize the histologic evaluation of hypophysectomy specimens, sections of 207 canine pituitary glands (196 postmortem, 11 hypophysectomy specimens) were reviewed. Adenohypophyseal proliferation was the most common ($n = 79$) lesion. Proliferative lesions were sparsely to densely granulated; the granules were usually basophilic to chromophobic and periodic acid-Schiff-positive. Adenohypophyseal proliferation was classified as hyperplasia ($n = 40$) if ≤2 mm diameter with intact reticulin network, as microadenoma ($n = 22$) for 1–5 mm homogeneous nodules with lost reticulin network, or as macroadenoma ($n = 17$) for larger tumors. Craniopharyngeal duct cysts were common incidental lesions and the only lesion in 15 dogs. Uncommon diagnoses included lymphoma ($n = 4$), hemorrhagic necrosis ($n = 4$), metastatic carcinoma ($n = 3$), hypophysitis ($n = 3$), ependymoma ($n = 2$), craniopharyngioma ($n = 2$), and 1 case each of metastatic melanoma, pituicytoma, gliomatosis, germ cell tumor, meningioma, and atrophy. The pituitary histologic diagnosis was associated with hyperadrenocorticism (HAC; $P < .001$) and adrenocortical histologic diagnosis ($P = .025$). Both HAC and adrenocortical hyperplasia showed a positive trend with the degree of adenohypophyseal proliferation. The association of adrenocortical hyperplasia with HAC was not significant ($P = .077$). Dogs with adenohypophyseal proliferations were older than dogs with normal pituitary glands ($P < .05$). Brachycephalic breeds were overrepresented among dogs with pituitary macroadenoma or craniopharyngeal duct cysts, but the association was not statistically significant ($P = .076$). Adenohypophyseal hyperplasia was more common than adenoma among postmortem specimens, but was unexpected in >80% of cases. Pituitary macroadenoma was the most common diagnosis in hypophysectomy specimens.

Keywords

adenohypophyseal hyperplasia, dogs, hyperadrenocorticism, pituitary adenoma, pituitary-dependent hypercortisolism, transsphenoidal hypophysectomy

The pituitary gland is capable of diverse responses to injury; however, in most species, the most common lesion is proliferation.[14,28] When functional, adenohypophyseal proliferations can result in dysfunction of secondary endocrine glands. Indeed, corticotroph adenoma is considered the most common cause of spontaneous canine hypercortisolism.[26] Until recently, the medical and surgical treatment of canine pituitary-dependent hypercortisolism (PDH) has been aimed mainly at the adrenal gland.[3,11,15,22] and histologic evaluation of canine pituitary glands has been predominantly a postmortem endeavor. In contrast, pituitary adenectomy or hypophysectomy is a mainstay in the treatment of human PDH (Cushing's disease) and other pituitary diseases, and surgical pathology is an important part of diagnosis and management.[2,4,5,22,24,27,29–31]

With improved imaging, microsurgical techniques, and postoperative care, transsphenoidal hypophysectomy has become a viable treatment option for canine pituitary disease, yet surgical pathology has been a minor component of most publications.[9,16,17,21,25] The main goal of this study was to classify canine pituitary lesions in archived case materials as the basis for development of a standardized approach to histologic evaluation of transsphenoidal hypophysectomy specimens. In addition to Sweet's reticulin histochemistry, and immunohistochemistry (IHC)[16] for adrenocorticotrophic hormone (ACTH), growth hormone (GH), melanocyte stimulating hormone (MSH), and Ki-67 (see online version for Supplemental Table S1). Adenomas that expressed only ACTH were classified as

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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.[1] 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.[2,3] 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.[2]

Two theories (hypothalamic and pituitary) have been proposed to explain the development of ACTH-producing pituitary tumors (corticotrophinomas).[4] The hypothalamic theory posits that the hypothalamus stimulates corticotrophs through enhanced secretion of corticotropin-releasing hormone and vasopressin.[5] 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.[6] A mutation in the glucocorticoid receptor gene results in a reduction in the number of DNA-binding sites while maintaining an affinity for cortisol.[7,8] This de novo mutation promotes a general resistance to glucocorticoids that precedes the formation of the corticotrophinoma. Studies[9,10] involving

ABBREVIATIONS

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

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CLINICAL RESEARCH

WILEY

Clinical characteristics and outcome in 15 dogs treated with transsphenoidal hypophysectomy for nonfunctional sellar masses

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Abstract

Objective: To characterize the clinical features, neurological examination findings, diagnostic imaging results, histopathological findings, and outcome following transsphenoidal hypophysectomy (TSH) in dogs with nonfunctional sellar masses (NFSM).

Study design: Multi-institutional retrospective study.

Methods: Medical records of dogs that underwent TSH for a NFSM were reviewed for clinical signs, physical and neurological examination findings, diagnostic imaging results, endocrine testing, surgery reports, and outcome. Magnetic resonance (MR) imaging was rereviewed, and tumors were classified using the previously described system according to pituitary tumor extension and vascular involvement. Owners of dogs that survived to discharge were contacted.

Results: The majority of dogs presented for mentation change (12/15). The mean pituitary to brain ratio (P/B ratio) was 1.05 (0.6–1.4). Eight dogs had a tumor imaging classification of 5B. Eleven dogs were diagnosed with a nonfunctional pituitary adenoma (NFPA). Perioperative mortality was 33% (5/15). The median survival for all dogs was 232 days (0–1658). When dogs that did not survive to discharge were excluded, the median survival time was 708 days.

Abbreviations: CDI, central diabetes insipidus; CPA, cardiopulmonary arrest; DTIC, dacarbazine; IRT, fractionated radiotherapy; IQR, interquartile range; IV, intravenous; KCS, keratoconjunctivitis sicca; MR, magnetic resonance; NFPA, non-functional pituitary adenoma; NFSM, non-functional sellar masses; PDH, pituitary-dependent hypercortisolism; PO, per os; PU/PD, polyuria and polydipsia; RT, radiation therapy; SD, standard deviation; TSH, Transsphenoidal hypophysectomy.

Presented in part at the 29th Symposium of the European Society of Veterinary Neurology-European College of Veterinary Neurology, Edinburgh, United Kingdom, September 16-17, 2016.

Brief Communication

Immunohistochemical Evaluation of Canine Pituitary Adenomas Obtained by Transsphenoidal Hypophysectomy

Veterinary Pathology
1–7

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Abstract

Hypophysectomy specimens from 16 dogs with pituitary adenoma were evaluated with periodic acid-Schiff (PAS), reticulin, and immunohistochemistry for adrenocorticotrophic hormone (ACTH), melanocyte stimulating hormone (MSH), growth hormone (GH), and Ki-67. The reticulin network was obliterated in all adenomas. One adenoma expressed ACTH and GH. Eight corticotroph adenomas were basophilic to chromophobic, and PAS- and ACTH-positive. Seven melanotroph adenomas were distinguished from corticotroph adenomas by expression of MSH. Pituitary-dependent hypercortisolism was diagnosed in 5 of 8 dogs with corticotroph and 4 of 7 with melanotroph adenoma. Pituitary height/brain area (P/B) ratio was elevated in all dogs. Previous canine hypophysectomy studies suggested that melanotroph adenomas were larger and carried a worse prognosis than corticotroph adenomas; however, in this study, corticotroph adenomas in comparison to melanotroph adenomas were larger (median P/B ratio: 1.06 versus 0.76), more proliferative (median Ki-67 index: 9.47% versus 1.99%), and associated with shorter survival (median: 300 versus 793 days). Recommended immunohistochemistry for PAS-positive pituitary adenomas includes ACTH and MSH to distinguish corticotrophs from melanotrophs and Ki-67 for proliferation index.

Keywords

corticotroph adenoma, dog, immunohistochemistry, melanotroph adenoma, pituitary adenoma, pituitary-dependent hypercortisolism, transsphenoidal hypophysectomy

Although proposed as a treatment for canine pituitary-dependent hypercortisolism (PDH) as early as 1968,[17] until the 1990s, canine hypophysectomy was mainly an experimental method to investigate pituitary function.[9] With improved diagnostic imaging, microsurgical techniques, and postoperative care, transsphenoidal hypophysectomy is increasingly used to treat canine PDH and other sellar diseases.[11,14] The purpose of this study was to characterize the histochemical and immunohistochemical features of canine pituitary adenoma in transsphenoidal hypophysectomy specimens. All 16 cases submitted to the Indiana Animal Disease Diagnostic Laboratory from 2011 to 2016 were included. These were a subset of 44 transsphenoidal hypophysectomies by author T.J.O.; 10 of the 16 cases were also part of another study.[16]

The criteria for inclusion were the presence of a sellar mass on magnetic resonance (MR) imaging, endocrine testing, knowledge of PDH diagnosis (yes/no), transsphenoidal hypophysectomy, histologic diagnosis of pituitary adenoma, and long-term follow-up. Each case was evaluated with hematoxylin and eosin (HE), periodic acid-Schiff (PAS), Gordon and

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Supplementary material for this article is available online.

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Oncology–Original Article

Feline Pituitary Adenomas: Correlation of Histologic and Immunohistochemical Characteristics With Clinical Findings and Case Outcome

Veterinary Pathology
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Abstract

Pituitary glands from 141 feline autopsy cases were reviewed histologically. Adenoma and hyperplasia were the most common lesions at 13 cases each. Pituitary adenoma was more likely than hyperplasia to be associated with clinical evidence of endocrinopathy or an intracranial mass ($P < .001$). A histochemical and immunohistochemical panel was applied to 44 autopsy- or hypophysectomy-derived pituitary adenomas in 43 cats from 2 diagnostic laboratories. Adenomas were differentiated from hyperplasia by the presence of disrupted reticulin fibers. One cat had a double (somatotroph and melanotroph) adenoma. Twenty somatotroph adenomas consisted of periodic acid-Schiff (PAS)-negative acidophils that expressed growth hormone; 16/20 had hypersomatotropism; 17/20 had diabetes mellitus. Eleven melanotroph adenomas consisted of PAS-positive basophils or chromophobes that expressed melanocyte-stimulating and adrenocorticotrophic hormones; 5/11 had hypercortisolism; 6/11 had diabetes mellitus. Eleven gonadotroph adenomas consisted of PAS-negative chromophobes that expressed follicle-stimulating and/or luteinizing hormones. Two thyrotroph adenomas consisted of PAS-negative basophils or chromophobes that expressed thyroid-stimulating hormone. Pituitary-dependent disease was not recognized in cats with gonadotroph or thyrotroph adenomas. The Ki-67 proliferation index in hypophysectomy specimens was lower in somatotroph than in melanotroph adenomas. Fourteen cats with hypophysectomy-treated somatotroph or melanotroph adenoma had an 899-day median survival time versus 173 days in 17 nonsurgical cases. After adjusting for age, adenoma size and type, hypophysectomized cats had an overall better survival time than nonsurgical cases ($P = .029$). The study results underscore the value of hypophysectomy and trophic hormone immunohistochemistry in the treatment and classification of feline pituitary adenomas.

Keywords

acromegaly, adenohypophyseal hyperplasia, cat, diabetes mellitus, feline diseases, hypercortisolism, hypersomatotropism, immunohistochemistry, pituitary adenoma, pituitary neuroendocrine tumor, transsphenoidal hypophysectomy

Proliferation (hyperplasia or neoplasia) is the most common pituitary lesion in domestic mammals.[25,26] However, in a review of pituitary glands from 65 feline autopsy cases,[36] only one proliferative lesion (hyperplasia) was encountered, and pituitary cysts, considered an incidental finding, were the most common lesion (8 cats). In a review of magnetic resonance (MR) images from 46 cats with histologically confirmed intracranial neoplasms, only 1 pituitary tumor was found.[47] Although pituitary neoplasia is uncommon in cats, pituitary tumors ($n = 14$) were still the third most common (after meningioma and lymphoma) in a review of 160 feline intracranial neoplasms.[48]

Tumors of the pituitary gland and sellar region account for 15% of human intracranial tumors, with pituitary adenoma being the most common skull-base tumor.[24,31,46] The 2017

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Research article

Related Commentary, page 4521

EGFR as a therapeutic target for human, canine, and mouse ACTH-secreting pituitary adenomas

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Cushing disease is a condition in which the pituitary gland releases excessive adrenocorticotropic hormone (ACTH) as a result of an adenoma arising from the ACTH-secreting cells in the anterior pituitary. ACTH-secreting pituitary adenomas lead to hypercortisolemia and cause significant morbidity and mortality. Pituitary-directed medications are mostly ineffective, and new treatment options are needed. As these tumors express EGFR, we tested whether EGFR might provide a therapeutic target for Cushing disease. Here, we show that in surgically resected human and canine corticotroph cultured tumors, blocking EGFR suppressed expression of proopiomelanocortin (*POMC*), the ACTH precursor. In mouse corticotroph EGFR transfectants, ACTH secretion was enhanced, and EGF increased *Pomc* promoter activity, an effect that was dependent on MAPK. Blocking EGFR activity with gefitinib, an EGFR tyrosine kinase inhibitor, attenuated *Pomc* expression, inhibited corticotroph tumor cell proliferation, and induced apoptosis. As predominantly nuclear EGFR expression was observed in canine and human corticotroph tumors, we preferentially targeted EGFR to mouse corticotroph cell nuclei, which resulted in higher *Pomc* expression and ACTH secretion, both of which were inhibited by gefitinib. In athymic nude mice, EGFR overexpression enhanced the growth of explanted ACTH-secreting tumors and further elevated serum corticosterone levels. Gefitinib treatment decreased both tumor size and corticosterone levels; it also reversed signs of hypercortisolemia, including elevated glucose levels and excess omental fat. These results indicate that inhibiting EGFR signaling may be a novel strategy for treating Cushing disease.

Introduction

Pituitary tumors, accounting for approximately 15% of intracranial tumors, are invariably benign monoclonal adenomas with excessive hormone secretion and/or tumor mass effects compressing vital structures (1). Adrenocorticotropic hormone–secreting (ACTH-secreting) tumors arising from pituitary corticotroph cells exhibit substantial morbidity and cause adrenal hypercortisolemia that results in osteoporosis, infections, psychiatric disorders, muscle atrophy, fat accumulation, hypertension, hyperglycemia, and ultimately death (2). The clinical syndrome of hypercortisolemia caused by ACTH-secreting pituitary tumor is known as Cushing disease.

No drug that effectively targets ACTH-secreting pituitary adenomas is currently approved (3, 4). Agents that inhibit adrenal cortisol synthesis have limited use due to side effects, moderate efficacy, and inability to target the pituitary tumor. Optimal treatment requires surgical adenoma resection, with initial remission rates achieved by experienced pituitary surgeons ranging 65%–90% for microadenomas, and less than 65% for macroadenomas (3). Postoperative recurrence rates at 10 years are 10%–20% for microadenomas and up to 45% for macroadenomas (3). Surgical cure is further challenged by the fact that preoperative pituitary tumor localization may be difficult, even using high-resolution MRI. More than 70% of ACTH-secreting tumors are less than 10 mm in size, and up to 50% of patients have no detectable tumor by MRI (5). Inferior petrosal sinus sampling of ACTH gradients, an invasive angiographic procedure, is frequently needed to confirm the presence of an ACTH-secreting pituitary tumor (6–8). Early results with the somatostatin analog pasireotide or the dopamine agonist cabergoline have shown short-term biochemical control in a minority of patients with Cushing disease (9, 10). Long-term side effects and efficacy of these medications in patients with Cushing disease are unknown, and pasireotide predisposes to hyperglycemia development (11). Clinical trials of retinoic acid in cancer Cushing disease have shown promise, but have not been extended to human use (12).

EGFR activation, resulting either from mutation or from ligand or receptor overexpression, is associated with a variety of human cancers (13). EGF is a pituitary cell growth factor and also directly induces prolactin synthesis (14). Although approximately 60% of pituitary tumors – including ACTH-secreting adenomas (40%–80%) – express EGFR (15–18), the role of the receptor in tumorigenesis remains unclear. In pituitary corticotroph tumors expressing EGFR, p27^{Kip1}, a cyclin-dependent kinase inhibitor, is downregulated (18). Mice with disrupted p27 also develop pituitary tumors mostly expressing proopiomelanocortin (POMC), a precursor protein of ACTH (19–22). We hypothesized that the receptor could be a novel target for therapy of Cushing disease, and therefore tested EGFR signaling in ACTH-secreting pituitary adenomas.

Gefitinib, a tyrosine kinase inhibitor (TKI) targeting the EGFR, blocks activity at the intracellular ATP-binding site of the tyrosine kinase domain (23). Gefitinib exhibits efficacy in treating pulmonary adenocarcinoma, especially in female Asian nonsmokers with deletion mutants of exon 19 (del746_A750) or point mutations of exon 21 (L858R) (24). Gefitinib is also effective in other cancers that overexpress EGFR (either WT or mutants; refs. 25, 26).

Conflict of interest: The authors have declared that no conflict of interest exists.
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Introduction

People:

- Third most common intracranial tumor (10-15%)
- Incidentaloma's in 1 in 6 adults (16 %)
- Clinically apparent tumor in 1 in 1000 adults
- Tumors causing Cushing's disease 1.2 – 2.4 per 1 million adults

Dogs:

- Tumors causing Cushing's disease 1.0 per 1,612 dogs
- 90,000 – 100,000 new cases/year

Cushing's in Man

ACTH Dependent	80%	
Pituitary adenoma		70%
Ectopic ACTH		10%
Ectopic CRH		
ACTH Independent	20%	
Adrenal adenoma		10%
Adrenal carcinoma		5%
Macronodular hyperplasia		1-2 %
McCune Albright		1-2 %
Primary pigmented nodular		1-2%

Cushing's in Dogs

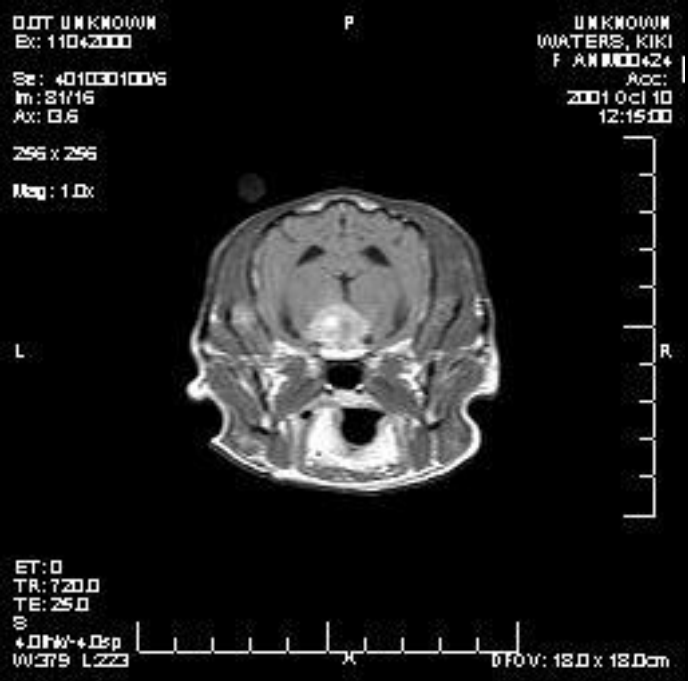
ACTH Dependent	85%	
Pars distalis		60%
Pars intermedia		25%
ACTH Independent	10%	
Adrenal adenoma		5%
Adrenal carcinoma		5%
Meal/Food Induced		
Ectopic		

Pathophysiology

Lack of diurnal variation of ACTH and cortisol in dogs and cats.

Episodic secretion of ACTH.

Estimated 90,000 – 100,000 new canine cases diagnosed per year.



Pathophysiology

Chronic hypercortisolemia results in clinical signs of Cushing's Disease

Pathophysiology

Pituitary carcinoma

Pituitary hyperplasia

Adenoma of pars distalis

~70% of dogs with PDH

Adenoma of pars intermedia

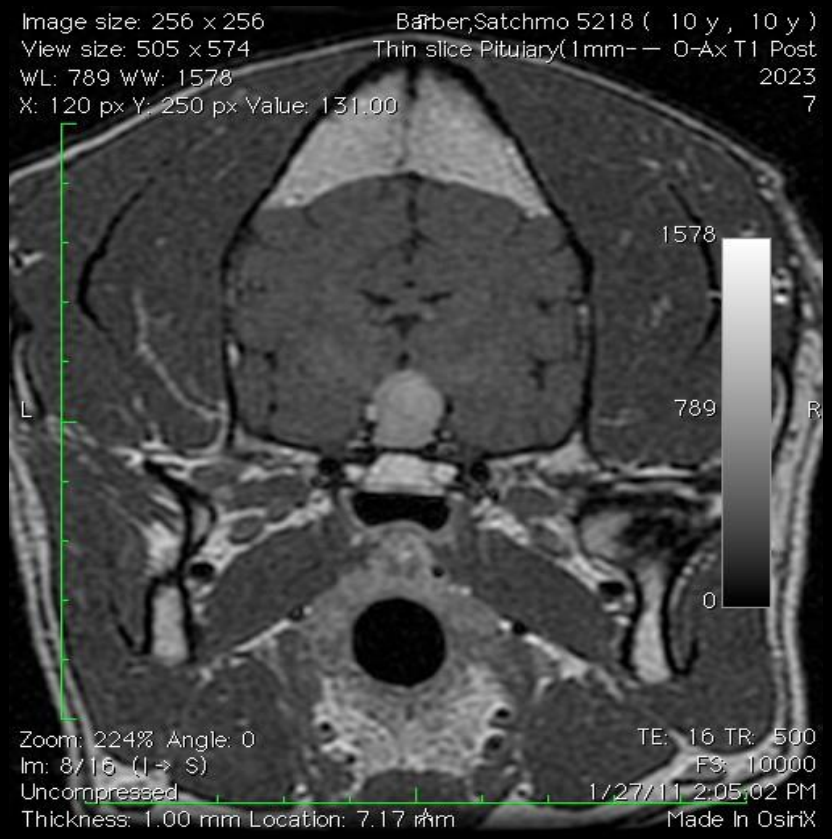
~ 20 - 30% of dogs with PDH

Normal Pituitary Size

P/B ratio < .31

Pituitary height

3.5 – 7 mm



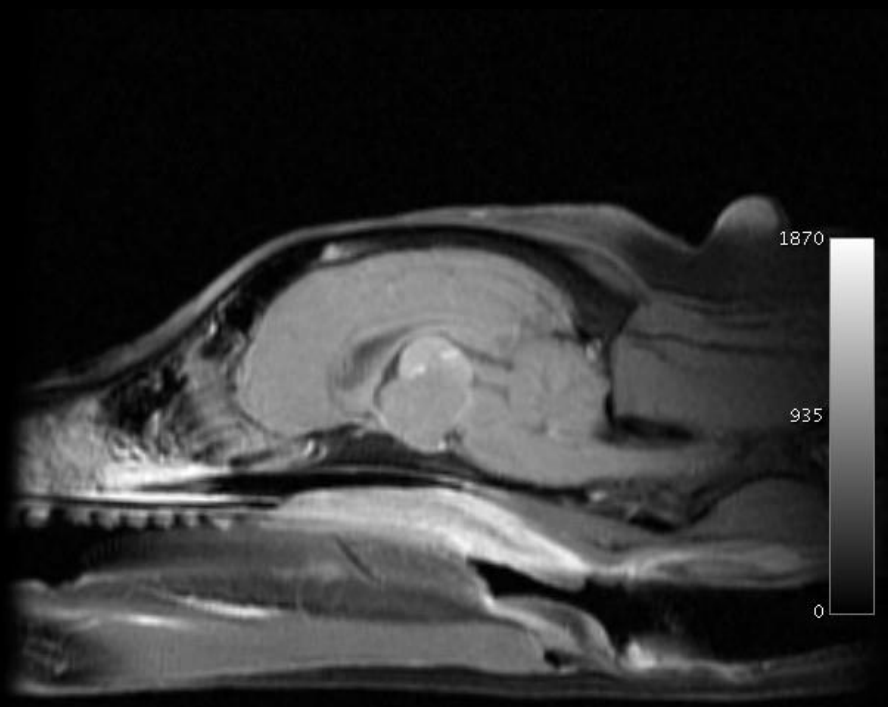
Pituitary Size

Enlarged in 55 – 68 %

P/B ratio .32 - .67

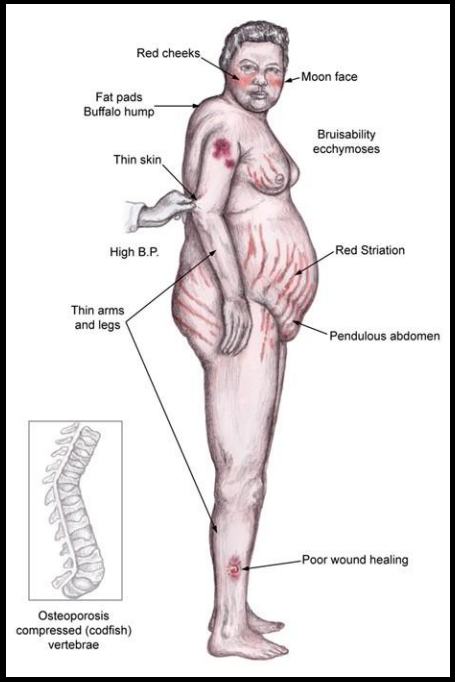
Tumors > 1 cm in 31 %

Neurologic signs with masses greater than 8.5 mm



Clinical Signs - Man

Obesity	39-96%
Facial plethora	82-90%
Decreased libido	24-90%
Muscle weakness	60-82%
Menstrual irregularity	74-80%
Glucose intolerance	50-80%
Hypertension	62-78%
Hirsutism	72-75%
Psychiatric disorders	53-70%



Clinical Signs - Dog

Polyuria	80%
Polydipsia	80%
Alopecia	80%
Polyphagia	70%
Hypertension	70%
Abdominal distention	60%
Panting	35 %
Obesity	25%
Behavior change	25%

Diagnosis- Man

Urinary free cortisol (UFC)
Late night salivary cortisol – outpatients
Midnight serum cortisol – inpatients
Dexamethasone suppression testing
    24 hour urine cortisol
    8 am serum cortisol

Minimum of 2 positive test results

Diagnosis - Dog

ACTH Stimulation Test
Low Dose Dexamethasone Suppression Test (LDDS)
Urine Cortisol:Creatinine Ratio (UCCR)
Salivary Free Cortisol Testing
Hair Cortisol Concentrations

Discriminatory Tests - Man

Plasma ACTH

Normal or high – ACTH dependent

Pituitary MRI

Low – ACTH independent

Adrenal imaging

ACTH Dependent – No pituitary mass

Bilateral IPSS to identify gradient. If no gradient:

Ectopic: CRH stim/HDDST, advanced imaging +/-scintigraphy

Discriminatory Tests - Dog

Most commonly used tests:

- ACTH concentrations
- HDDST
- Ultrasonic examination of adrenal glands
  - 2-3 % incidence of incidentaloma
- MRI

Etiology of PDH

Complex

Not completely understood

Theories:

- Evidence in man supports a primary pituitary abnormality
- Most evidence in dogs supports a hypothalamic disorder

Etiology of PDH

Screening for Genetic Mutations in Canine PDH

Gs alpha
H-, K-, N-ras genes
DNA-binding domain of the glucocorticoid receptor
Tpit

No differences between control and affected dogs

Etiology of PDH

Recent evidence suggests dopamine may play a role in regulation of the hypothalamic pituitary adrenal (HPA) axis

Dopamine inhibits secretion of ACTH primarily from the pars intermedia

Dopamine appears to have an inhibitory effect on proopiomelanocortin, a precursor of ACTH in the pars distalis

The Case of the Frozen Addicts

How the solution of an extraordinary medical mystery spawned a revolution in the understanding and treatment of Parkinson's disease

J. William Langston, M.D.
and Jon Palfreman

Clinical Signs of Canine Cushing's Disease

- Polyuria
- Polydipsia
- Polyphagia
- Abdominal distention
- Panting
- Obesity or redistribution of body fat

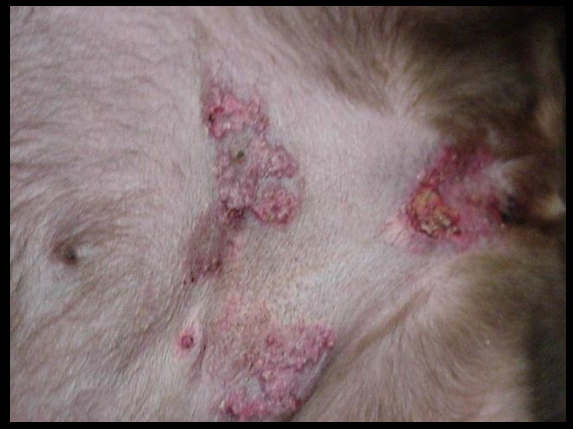
Clinical Signs of Canine Cushing's Disease

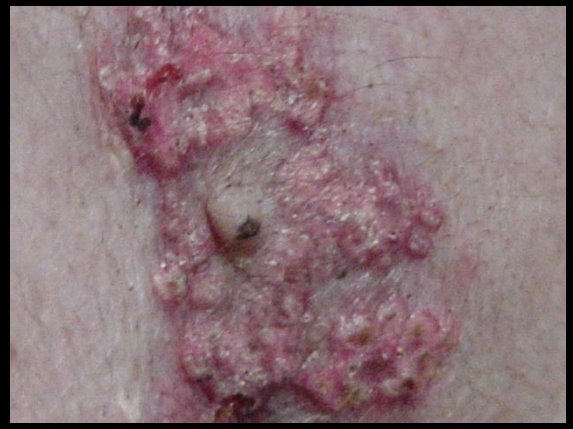
- Change in activity level
- Decreased exercise tolerance
- Anestrus
- Testicular atrophy

Clinical Signs of Canine Cushing's Disease

Dermatologic

Alopecia
Cutaneous hyperpigmentation
Calcinosis cutis
Pyoderma
Comedones





Clinical Signs of Canine Cushing's Disease

Behavioral signs:

Change in greeting behavior
Change in activity level
Change in responsiveness
Abnormal sleep/wake cycles

Diagnosis of Canine Cushing's Disease

Minimum data base

- Pertinent history and clinical signs
- Serum chemistries, complete blood count
- Urinalysis
- Urine culture

Supplemental Tests

- Abdominal radiographs $\pm$ ultrasound

Diagnosis of Canine Cushing's Disease

ACTH Stimulation Test
Low Dose Dexamethasone Suppression Test (LDDS)
Urine Cortisol:Creatinine Ratio (UCCR)
Salivary Free Cortisol Testing
Hair Cortisol Concentrations

Screening Tests

Low Dose Dexamethasone Suppression Test

- Diagnostic in 90% of dogs with PDH or ADH
- Requires 8 hour testing period
- Cannot be used to diagnose iatrogenic Cushing's disease

Screening Tests

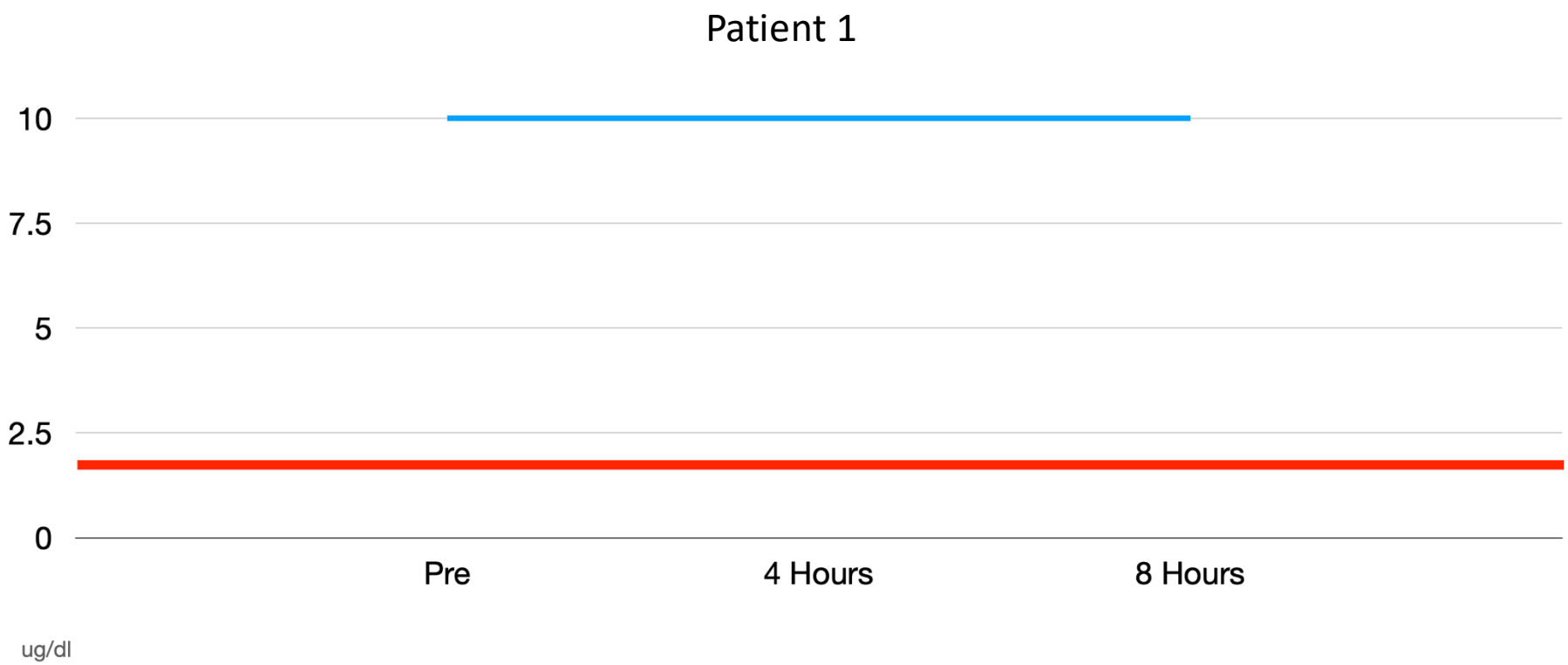
LDDS

Elevated 8 hour sample = HAC

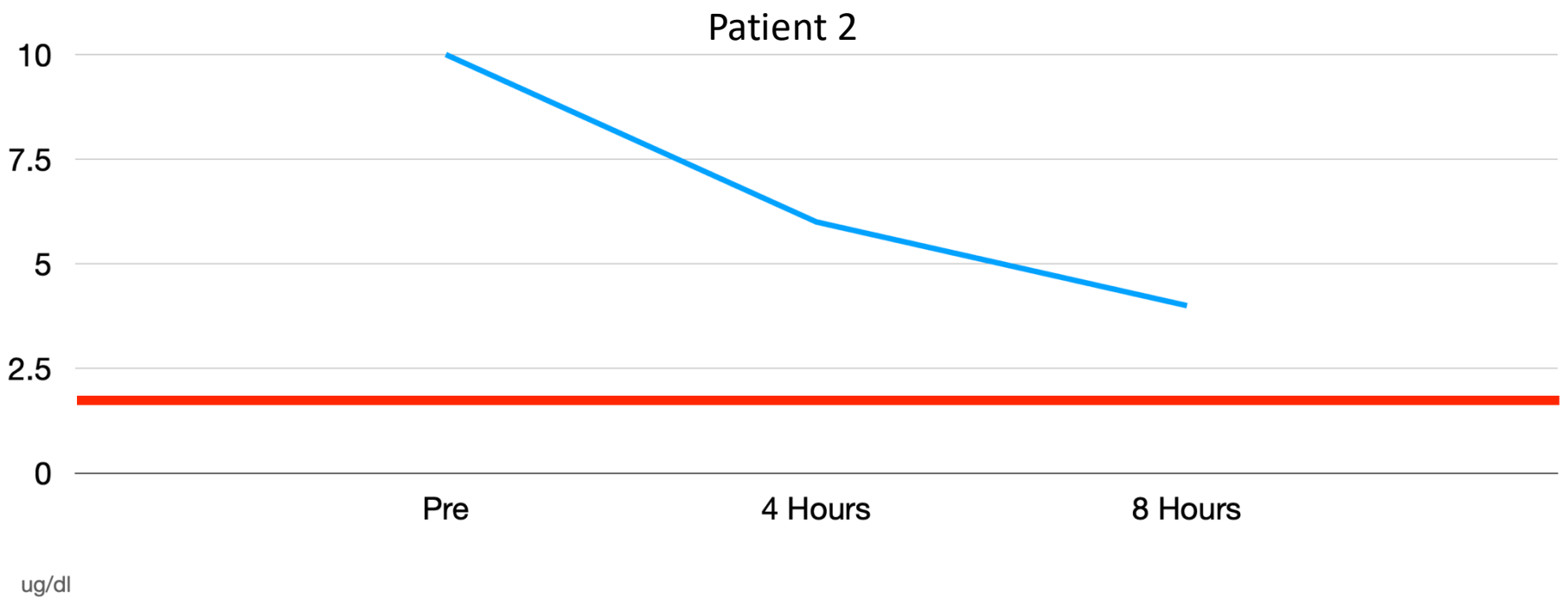
Compare 4 and 8 hour levels to Pre

50% suppression = PDH

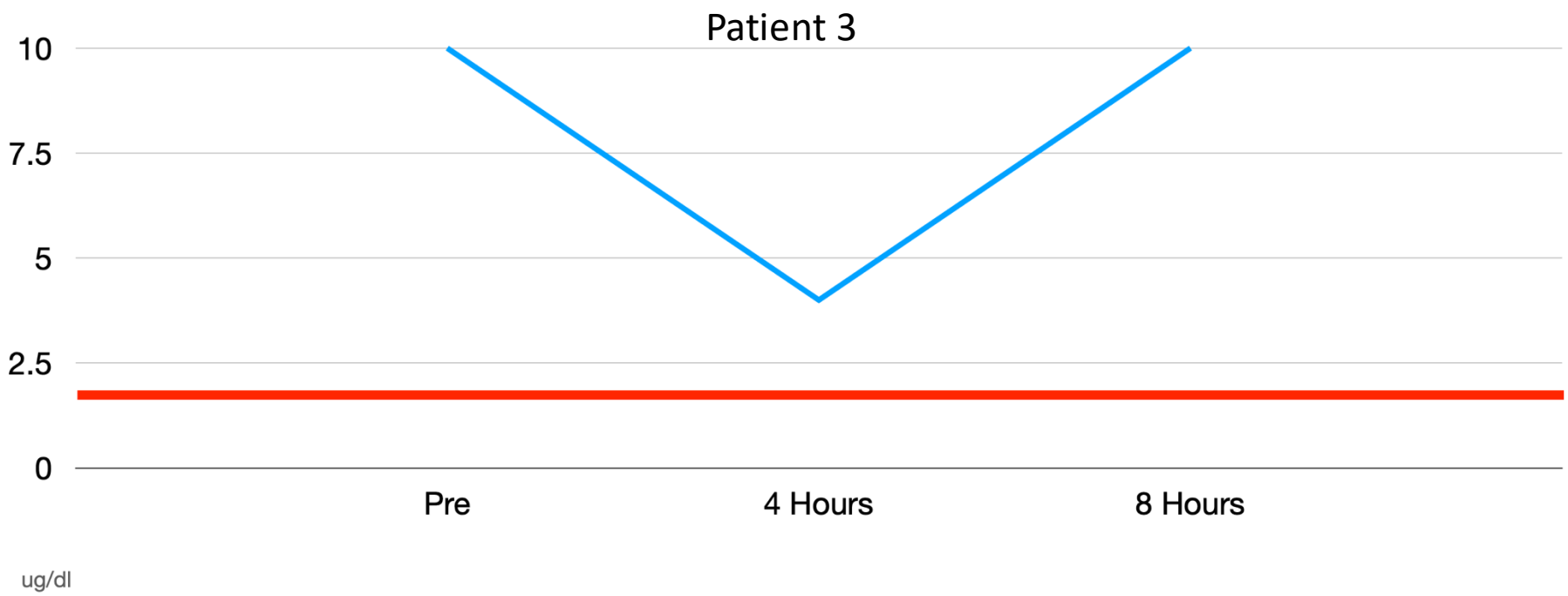
Screening Tests



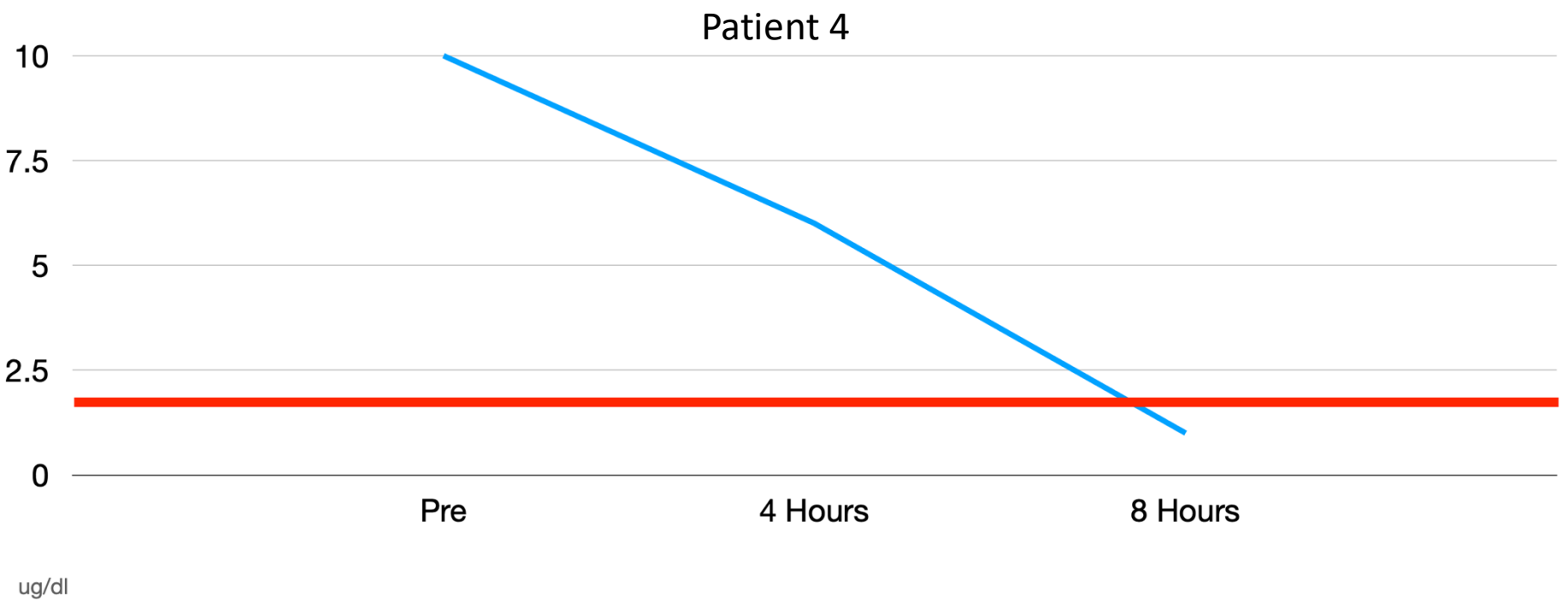
Screening Tests



Screening Tests



Screening Tests



Screening Tests

ACTH Stimulation Test

- Diagnostic in 80-85% of dogs with PDH or ADH
- Can be used to diagnose iatrogenic Cushing's
- Requires a baseline sample and 1 hour (Cortrosyn) or 2 hour (IM gel) sample post ACTH administration

Screening Tests

Urine Cortisol:Creatinine Ratio

- Sampling errors
- High sensitivity
- Low specificity
- High number of false positives

PDH VS ADH

Most commonly used tests:

- High Dose Dexamethasone Suppression Test
- Endogenous ACTH concentrations
- Ultrasonic examination of adrenal glands

High Dose Dexamethasone Suppression Test

Key Points:

100% of dogs with ADH will not suppress

75% of dogs with PDH will suppress

25% of PDH dogs will not suppress

Therefore lack of suppression is non-diagnostic

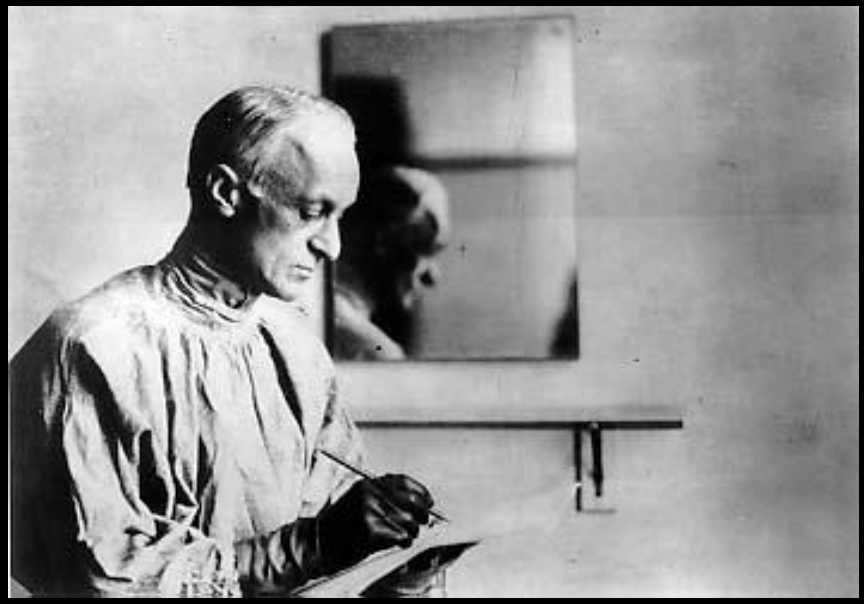
Endogenous ACTH

PDH dogs should have normal or increased ACTH concentrations

ADH dogs should have decreased ACTH concentrations

Some overlap occurs with normal dogs

Deciding on
Treatment Options



Treatment Options for PDH

o,p' DDD - Lysodren

l-deprenyl - Anipryl

Trilostane – Modrenal, Vetoryl

Ketoconazole – Nizoral

Bromocriptine

Metyrapone - Metopirone

Trilostane

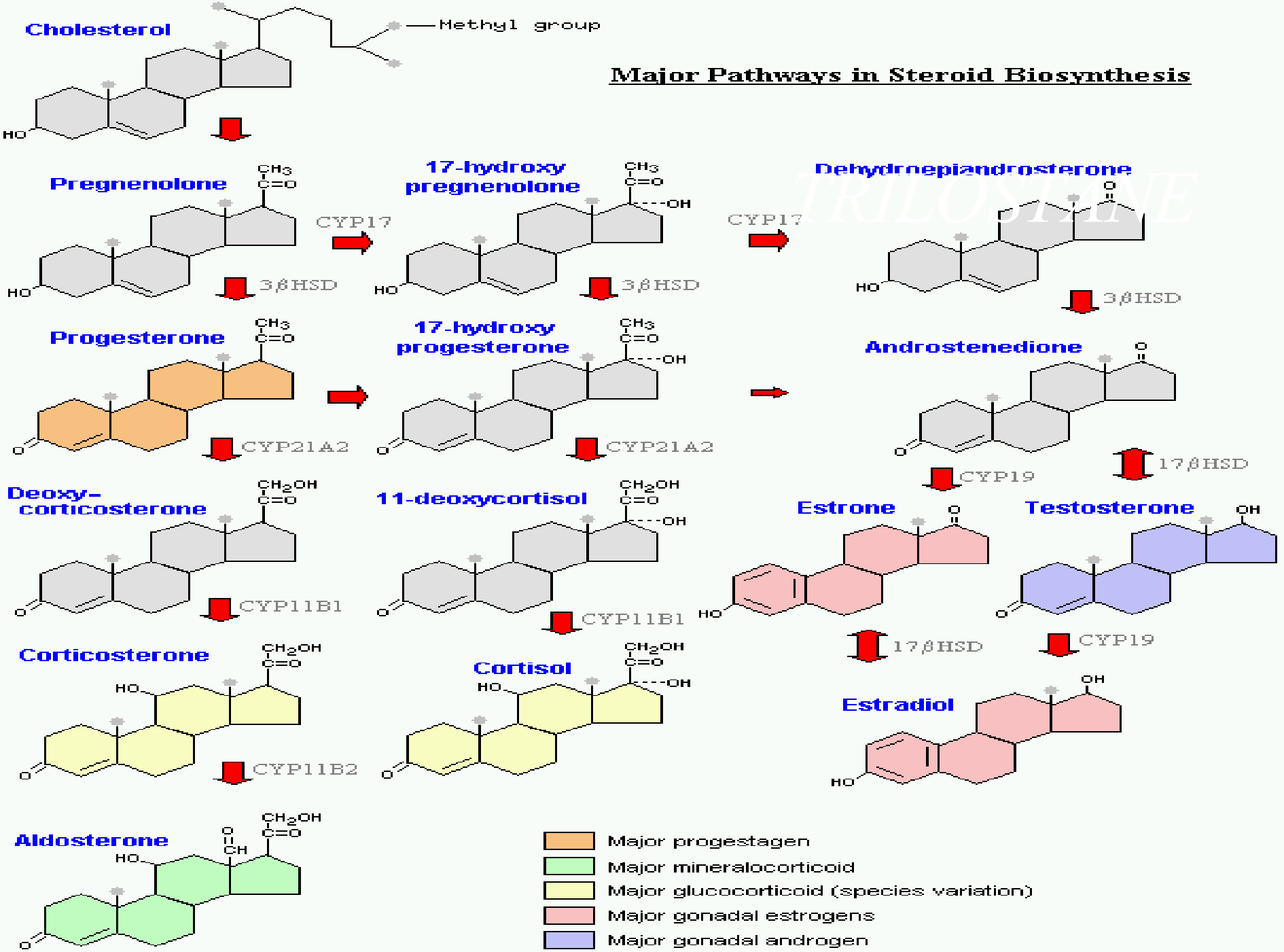
Adrenal enzyme inhibitor

- Similar to ketoconazole and metyrapone

Inhibitor of 3β-hydroxylase

- Rapid reductions in cortisol concentrations
- May also affect aldosterone concentrations
  - ↑ K and ↓ Na concentrations

Major Pathways in Steroid Biosynthesis

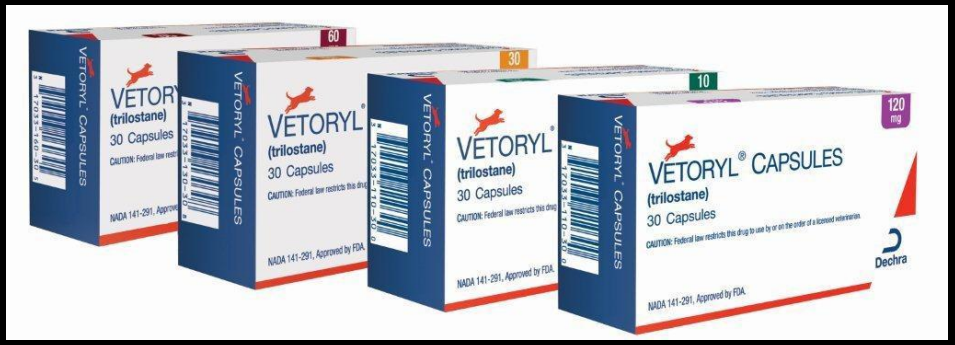


Trilostane

Product Characteristics

5 , 10, 30mg, 60 and 120 mg capsules

Blister packs of 30

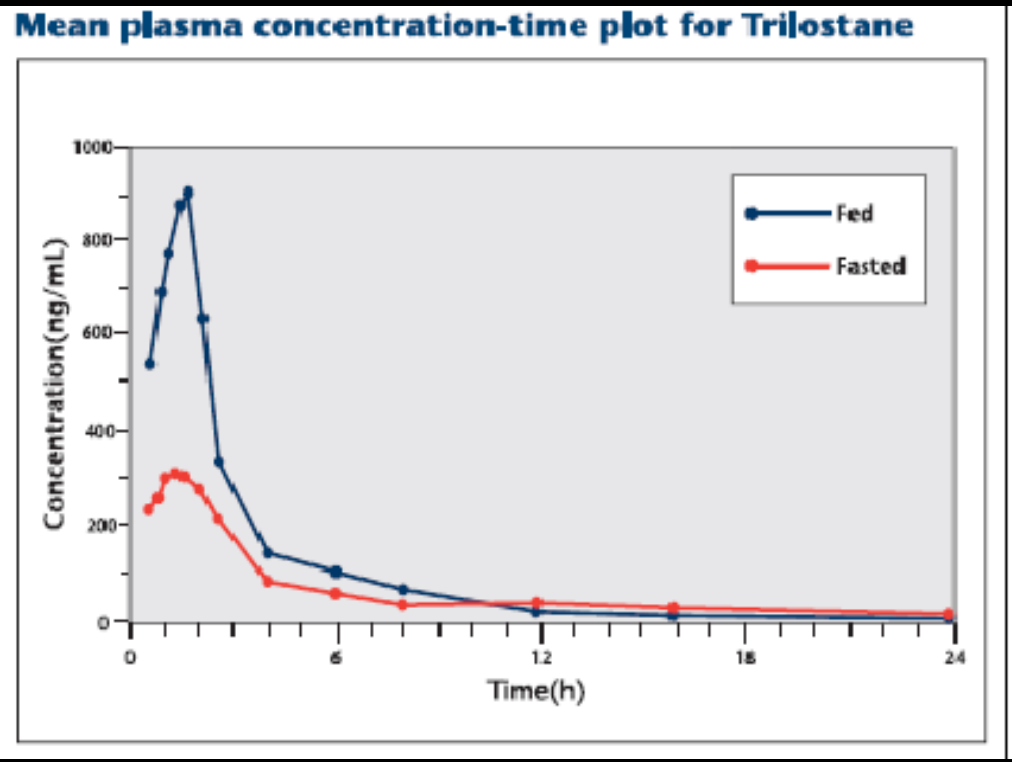


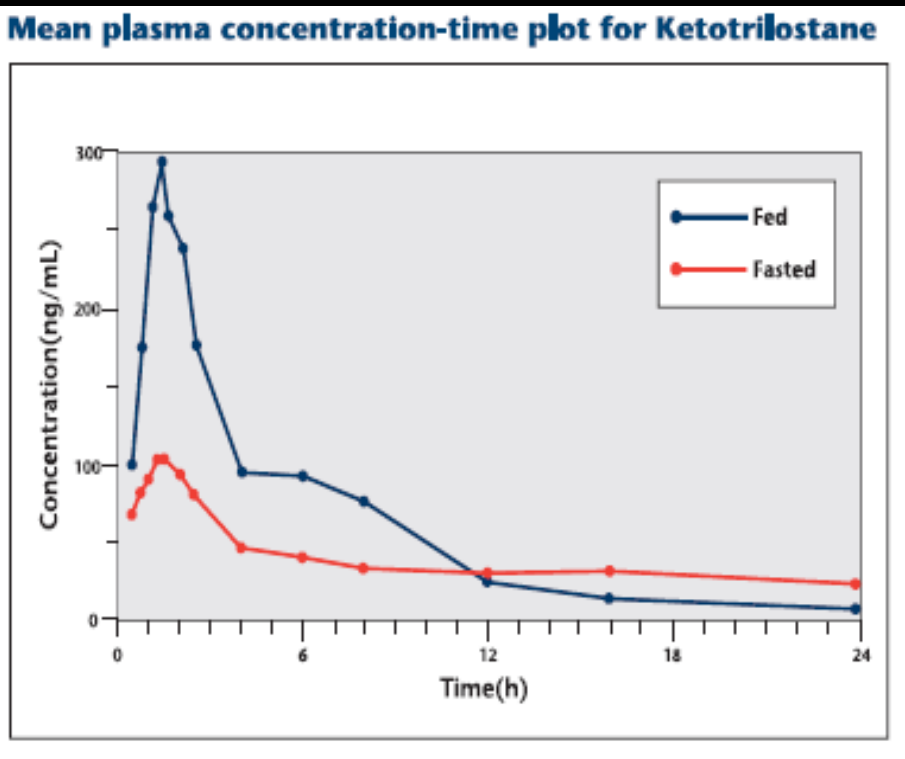
Dose 1-2 mg/kg SID

Ideally start LOW

Dose in morning – easier for monitoring

Trilostane

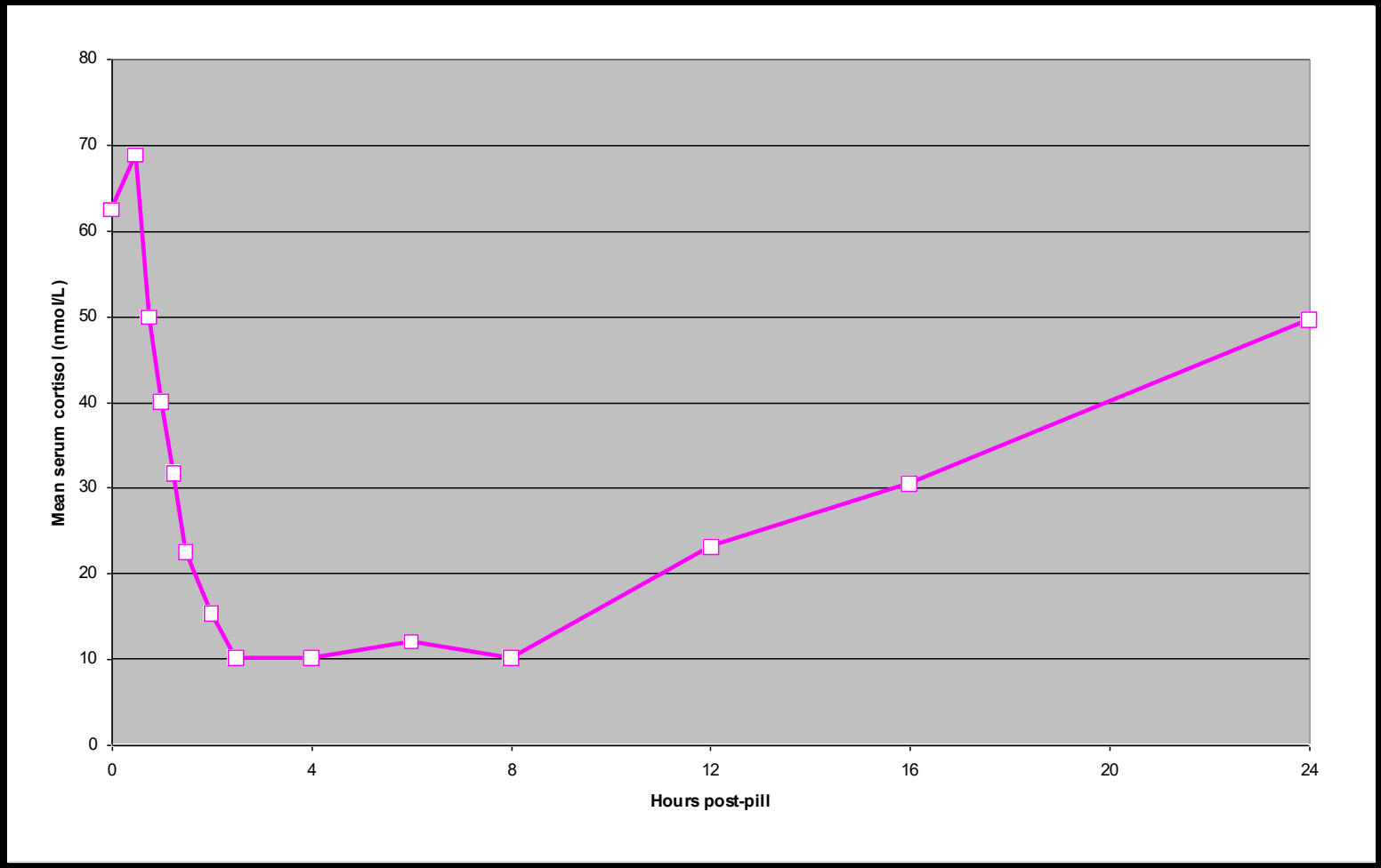




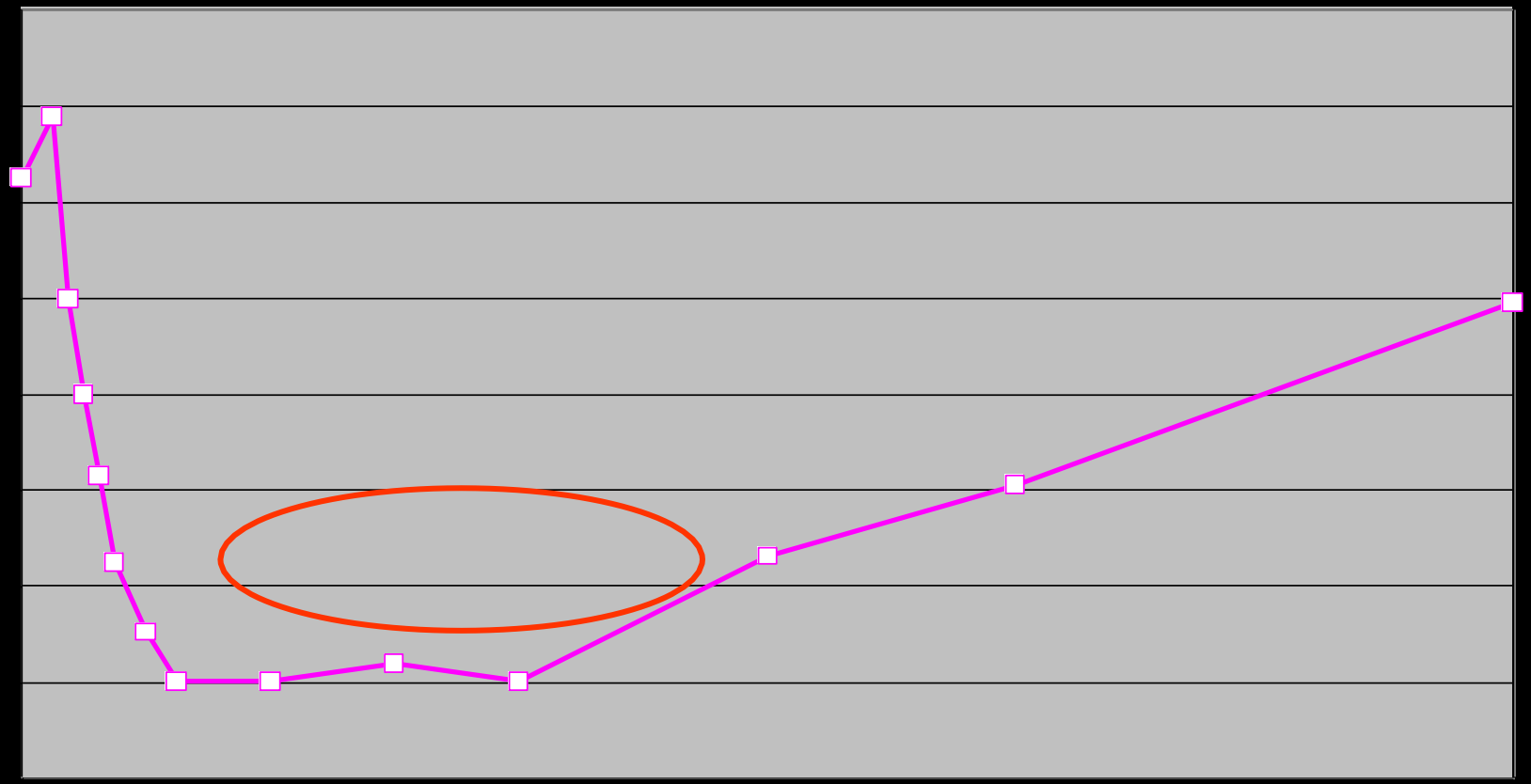
Rapidly absorbed from the gastrointestinal tract

Dosing with food significantly t rate & extent of absorption

Trilostane


Mean serum cortisol (nmol/L)
80
70
60
50
40
30
20
10
0
0
4
8
12
16
20
24
Hours post-pill

Trilostane



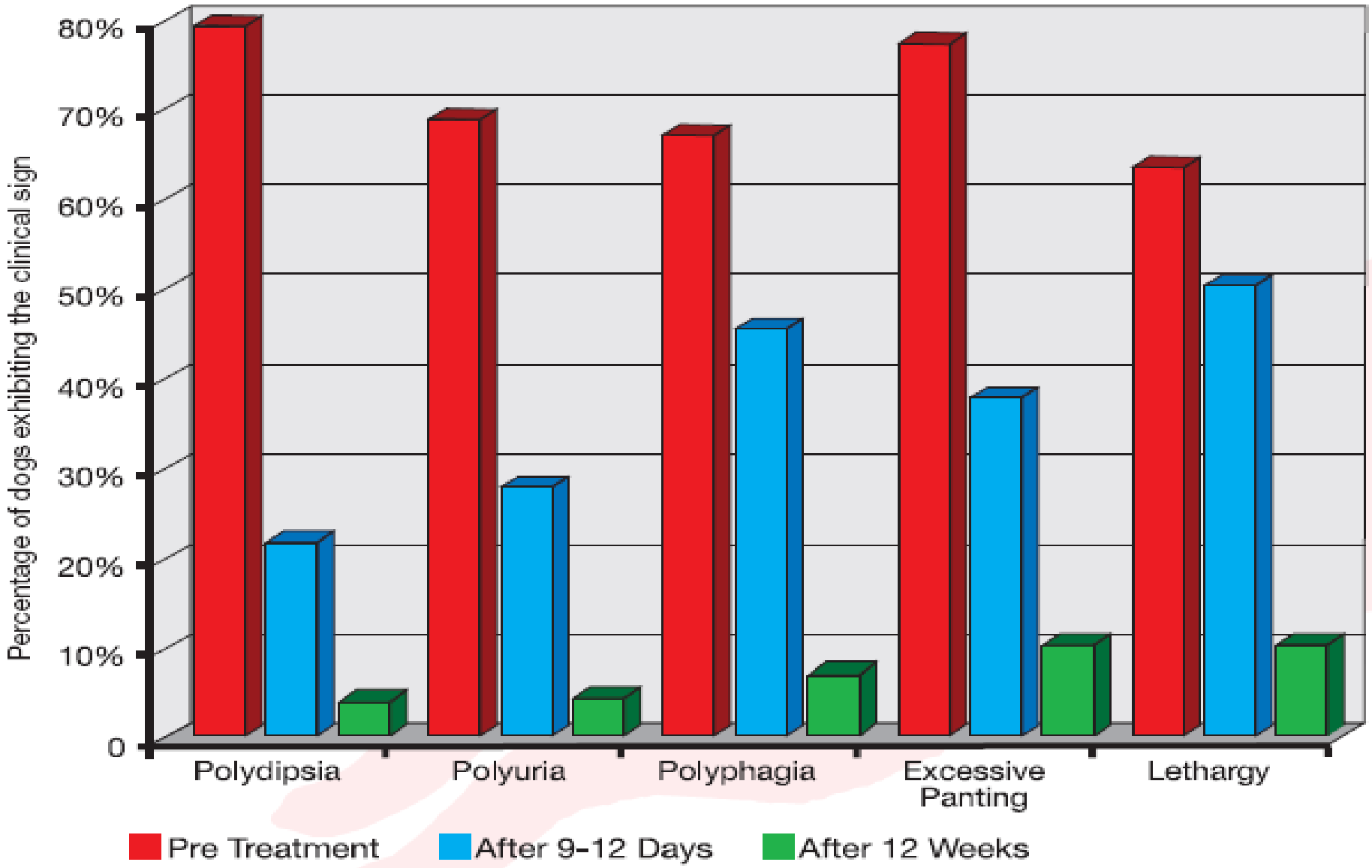
Monitoring

Electrolytes & ACTH stimulation test (4-6 hours post dosing)

- Pre-treatment
- 10 days, 4 weeks, 12 weeks
- Every 3 months
- Each dose adjustment

Assess clinical signs

SURVEY OF OWNER PERCEPTIONS OF CHANGES IN CLINICAL SIGNS[4]



Adverse Reactions

Rare reports of adrenal necrosis

- Mediated by rising ACTH levels

Unmask arthritis or inflammatory dermatitis

Sudden death

US Clinical Study

107 dogs enrolled (103 were deemed evaluable)

- Age range 6-16 years
- Body weight 3-53.5 kg

224 dogs screened

- 95 dogs w/ PDH; 5 dogs w/ FAT
  - 1 dog PDH + FAT
  - 6 dogs inconclusive localization

US Clinical Study

Conclusion –highly effective

- 77.3% success

Success criteria

- Post-ACTH stim <9.1 ug/dL
- Clinical improvement

Monitoring

Resting cortisol ?

Post-ACTH cortisol 1.5 - 9.1 μg/dL

Some recommend < 5.4 ug/dl
(4-6 hrs post dosing)

Optimizing Treatment

Increase in once daily dose required if:

Clinical signs not controlled

Post-ACTH cortisol > 9.1 ug/dl
(performed 4-6 hrs after dosing)

Optimizing Treatment

Twice daily dosing may be required if:

1. Clinical signs not controlled
2. 4 hour post-ACTH cortisol < 9.1 ug/dl and
3. ACTH stimulation test 22-24 hrs after dosing

   Post-ACTH cortisol > 9.1 ug/dl

Value of ACTH Stimulation Testing ?

Pre-Vetoryl Cortisol: an improved monitoring protocol

Developed by Ian Ramsey BVSc, PhD, DSAM, Dipl. ECVIM-CA, FHEA, MRCVS, Federico Fracassi DVM, PhD, Dipl. ECVIM-CA, Nadja Sieber-Ruckstuhl PhD, Dr. med. vet, Dipl. ACVIM, Dipl. ECVIM-CA

History and clinical examination

The most important factor to consider when re-evaluating a dog receiving Vetoryl is to carefully consult with the owner regarding the dog's clinical response at home. This critical part of the assessment is often overlooked in a busy clinic but is vital to ensure good compliance, safety and optimal response to therapy.

Owners reporting at any time that their dog is unwell should be seen at their veterinary practice so that iatrogenic hypoadrenocorticism can be investigated (through cortisol results and the results of haematology, biochemistry and electrolyte analysis).

Pre-Vetoryl Cortisol

Suitable dogs

- Once- or twice-daily Vetoryl dosing
- Adrenal- or pituitary-dependent hyperadrenocorticism (HAC)
- Clinically well dogs (with or without signs of HAC)
- Calm dogs

Unsuitable dogs

- Aggressive dogs
- Stressed dogs (e.g. persistently barking)
- Unwell dogs

Appointment

- Book an appointment just before the next Vetoryl dose is due
- If the dog is normally given Vetoryl at an inconvenient time (e.g. 6 am) then ask owner to give at a convenient time from at least the day before (e.g. 9 am)
- Make sure owner has not given Vetoryl and that nothing stressful has happened that morning (e.g. vomiting, injury)
- Ensure the owner has completed the Quality of Life Questionnaire
- Take history* and examine the dog, checking for signs of HAC

Sample

- Take sample immediately after examination and before administration of Vetoryl
- 1 to 2 ml of blood in heparin or serum tube
- Can be separated and stored for up to 1 week
- Send to an external laboratory participating in an external quality assurance scheme (e.g. ESVE- or SCE- programmes) and preferably that uses a Siemens IMMULITE® – or a method that has been validated against this machine

VETORYL®

Life restored on every level

Pre-Vetoryl Cortisol: an improved monitoring protocol

Day 1
Vetoryl starting dose is approximately 2 mg/kg
Administer orally, once daily, with food

Day 10
History + Clinical examination

Clinically well

Continue Vetoryl treatment at current dose

Day 28
History +
Clinical examination

Clinically unwell

Stop Vetoryl treatment

Pre- and Post-ACTH Stimulation Test cortisols & analysis of serum electrolytes (in particular Na and K) immediately

Pre- **and** Post-ACTH Stimulation cortisols <1.5 ug/dl

Pre- **or** Post-ACTH Stimulation cortisols >1.5 ug/dl

Clinical signs probably due to hypocortisolism or hypoadrenocorticism
Treat symptomatically as required[5]

Unlikely to be hypocortisolism
Investigate other causes

Restart Vetoryl at lower dose when clinical signs of HAC recur or Post-ACTH cortisol > 5 ug/dl

Restart Vetoryl when well

RETURN TO DAY 1

Clinical signs of HAC[1]

Pre-Vetoryl Cortisol*

1.5 ug/dl — 5.0 ± 15% ug/dl

No clinical signs of HAC

Pre-Vetoryl Cortisol*

0 ug/dl — 1.5 ug/dl — 5.0 ± 15% ug/dl

If Pre-Vetoryl Cortisol values do not match the clinical picture contact Dechra Technical Services

Increase dose frequency[3]
or
Increase dose[4]

Re-evaluate case[2]
Consider lower dose[4]

Continue Vetoryl treatment at current dose

Re-evaluate case
Consider dividing current dose equally between morning and evening doses
If already dosing twice daily then consider small dose increase[4]

RETURN TO DAY 1

RE-EXAMINE IN 3 MONTHS AND RETURN TO DAY 28

RETURN TO DAY 1

Trilostane

Twice a day dosing

0.2 – 2.5 mg/kg q 12 hours

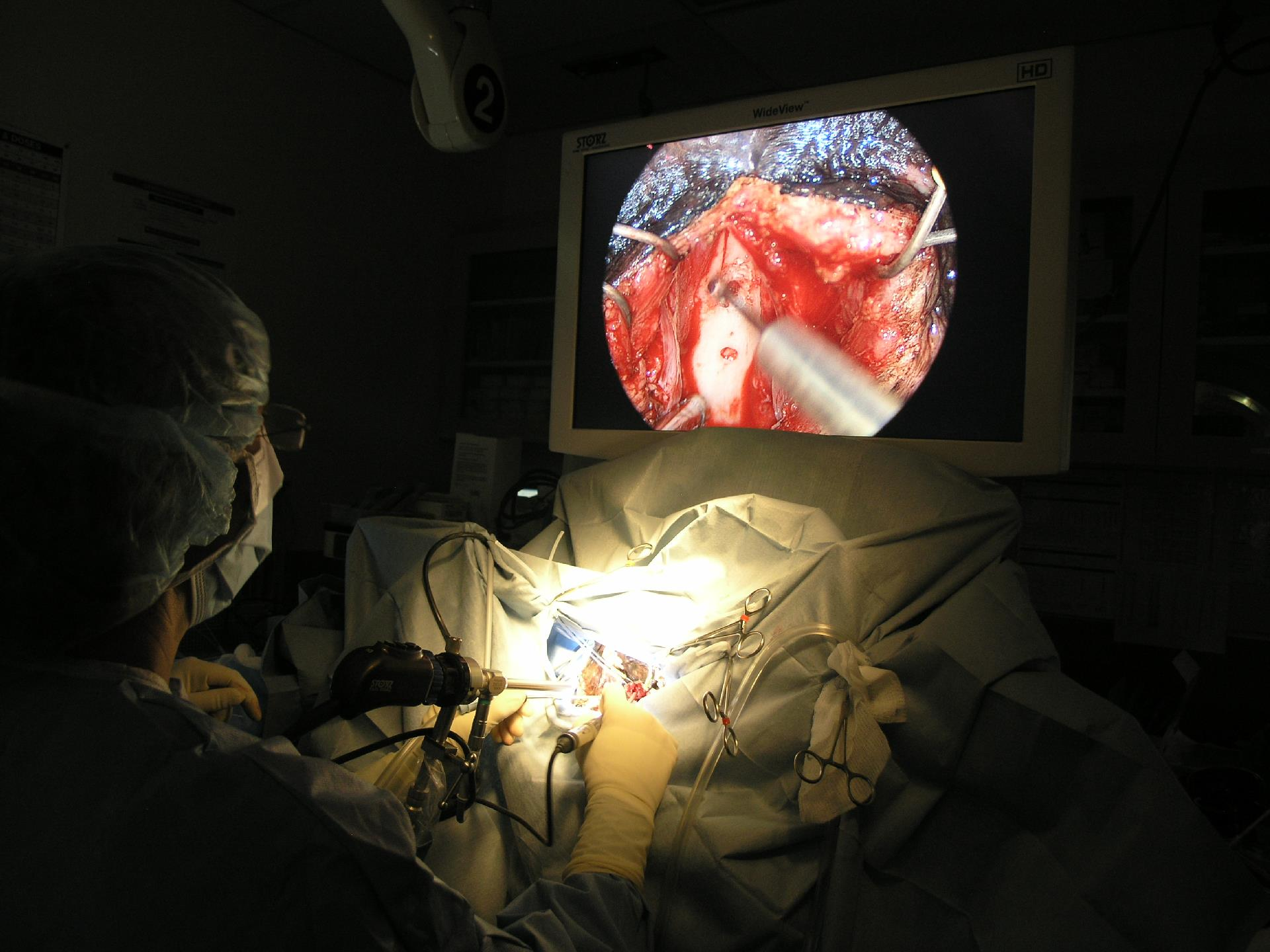
3.0 – 3.5 mg/kg q 12 hours

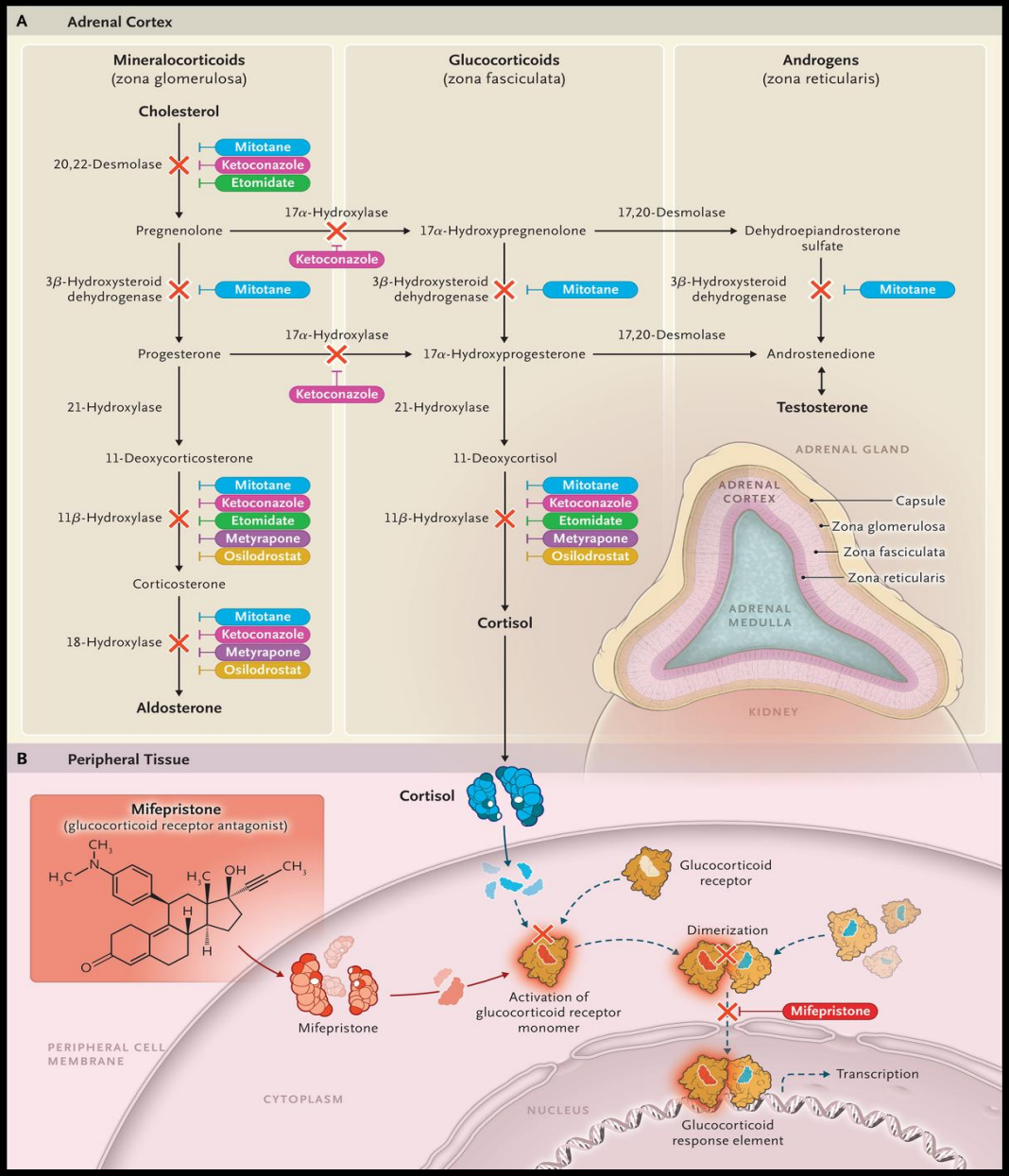
Trilostane vs Lysodren

Survival Times

- Lysodren
  - 750 days
  - 720 days (non-selective)
- Trilostane
  - 930 days (BID)
  - 900 days (qD)
  - 662 (qD)

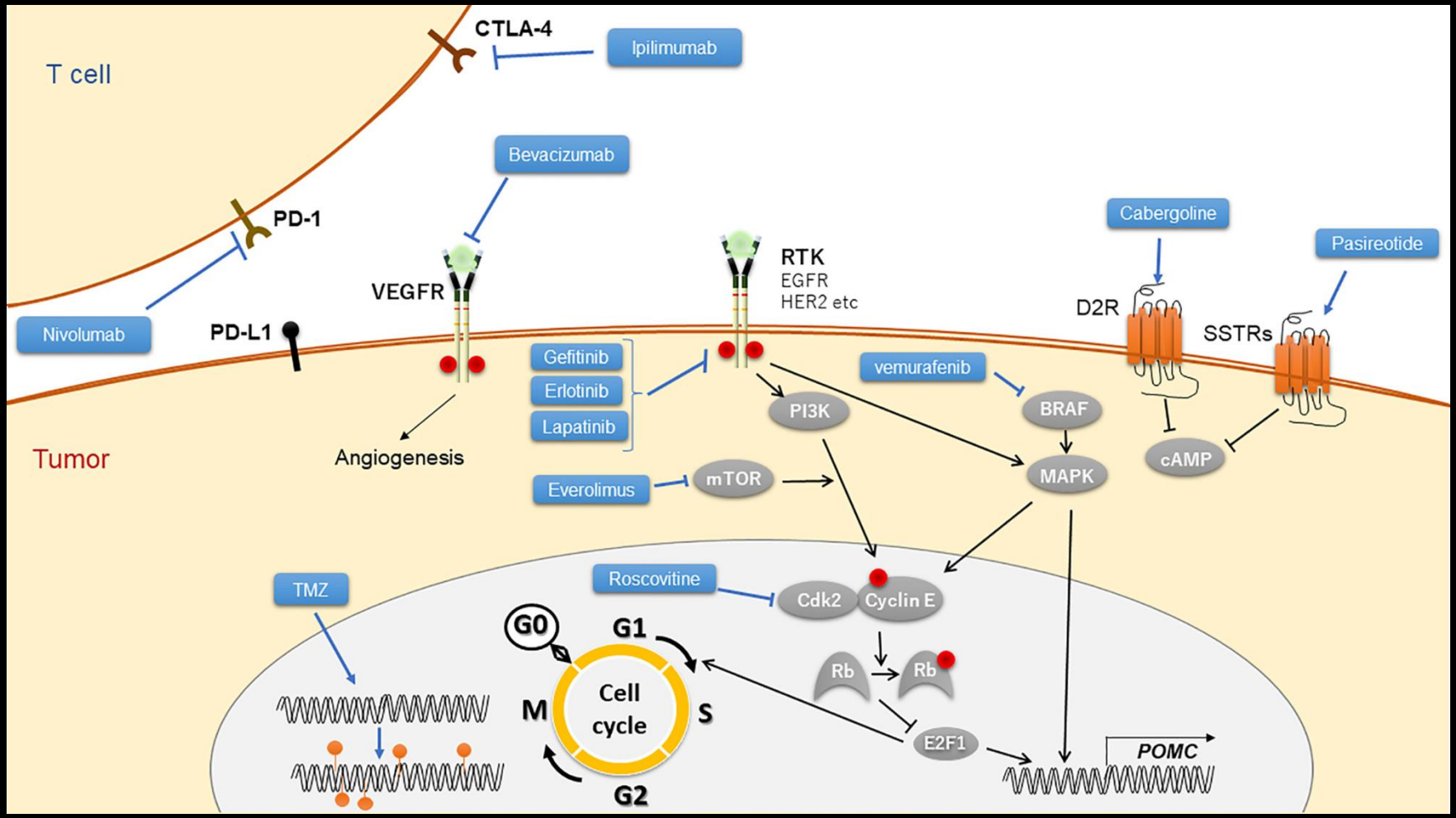

Vacuum


STORZ
WideView
HD



CW Vokoun et al. N Engl J Med 2023;388:165-175.

The NEW ENGLAND JOURNAL of MEDICINE


T cell
CTLA-4
Ipilimumab
Bevacizumab
PD-1
Nivolumab
PD-L1
VEGFR
RTK
EGFR
HER2 etc
Cabergoline
Pasireotide
D2R
SSTRs
Gefitinib
Erlotinib
Lapatinib
vemurafenib
PI3K
BRAF
MAPK
cAMP
Tumor
Angiogenesis
Everolimus
mTOR
TMZ
Roscovitine
Cdk2
Cyclin E
G0
G1
S
G2
M
Cell cycle
Rb
Rb
E2F1
POMC

 Related Commentary, page 4621

EGFR as a therapeutic target for human, canine, and mouse ACTH-secreting pituitary adenomas

Hidenori Fukuoka,[1] Odelia Cooper,[1] Anat Ben-Shlomo,[1] Adam Mamelak,[1,2] Song-Guang Ren,[1] Dave Bruyette,[3] and Shlomo Melmed[1]

[1]Pituitary Center, Department of Medicine, and [2]Department of Neurosurgery, Cedars-Sinai Medical Center, Los Angeles, California, USA. [3]VCA West Los Angeles Animal Hospital, Los Angeles, California, USA.

Cushing disease is a condition in which the pituitary gland releases excessive adrenocorticotropic hormone (ACTH) as a result of an adenoma arising from the ACTH-secreting cells in the anterior pituitary. ACTH-secreting pituitary adenomas lead to hypercortisolemia and cause significant morbidity and mortality. Pituitary-directed medications are mostly ineffective, and new treatment options are needed. As these tumors express EGFR, we tested whether EGFR might provide a therapeutic target for Cushing disease. Here, we show that in surgically resected human and canine corticotroph cultured tumors, blocking EGFR suppressed expression of proopiomelanocortin (*POMC*), the ACTH precursor. In mouse corticotroph EGFR transfectants, ACTH secretion was enhanced, and EGF increased *Pomc* promoter activity, an effect that was dependent on MAPK. Blocking EGFR activity with gefitinib, an EGFR tyrosine kinase inhibitor, attenuated *Pomc* expression, inhibited corticotroph tumor cell proliferation, and induced apoptosis. As predominantly nuclear EGFR expression was observed in canine and human corticotroph tumors, we preferentially targeted EGFR to mouse corticotroph cell nuclei, which resulted in higher *Pomc* expression and ACTH secretion, both of which were inhibited by gefitinib. In athymic nude mice, EGFR overexpression enhanced the growth of explanted ACTH-secreting tumors and further elevated serum corticosterone levels. Gefitinib treatment decreased both tumor size and corticosterone levels; it also reversed signs of hypercortisolemia, including elevated glucose levels and excess omental fat. These results indicate that inhibiting EGFR signaling may be a novel strategy for treating Cushing disease.

Introduction

Pituitary tumors, accounting for approximately 15% of intracranial tumors, are invariably benign monoclonal adenomas with excessive hormone secretion and/or tumor mass effects compressing vital structures (1). Adrenocorticotropic hormone–secreting (ACTH-secreting) tumors arising from pituitary corticotroph cells exhibit substantial morbidity and cause adrenal hypercortisolemia that results in osteoporosis, infections, psychiatric disorders, muscle atrophy, fat accumulation, hypertension, hyperglycemia, and ultimately death (2). The clinical syndrome of hypercortisolemia caused by ACTH-secreting pituitary tumor is known as Cushing disease.

No drug that effectively targets ACTH-secreting pituitary adenomas is currently approved (3, 4). Agents that inhibit adrenal cortisol synthesis have limited use due to side effects, moderate efficacy, and inability to target the pituitary tumor. Optimal treatment requires surgical adenoma resection, with initial remission rates achieved by experienced pituitary surgeons ranging 65%–90% for microadenomas, and less than 65% for macroadenomas (3). Postoperative recurrence rates at 10 years are 10%–20% for microadenomas and up to 45% for macroadenomas (3). Surgical cure is further challenged by the fact that preoperative pituitary tumor localization may be difficult, even using high-resolution MRI. More than 70% of ACTH-secreting tumors are less than 10 mm in size, and up to 50% of patients have no detectable tumor by MRI (5). Inferior petrosal sinus sampling of ACTH gradients, an invasive angiographic procedure, is frequently needed to confirm the presence of an ACTH-secreting pituitary tumor (6–8). Early results with the somatostatin analog pasireotide or the dopamine agonist cabergoline have shown short-term biochemical control in a minority of patients with Cushing disease (9, 10). Long-term side effects and efficacy of these medications in patients with Cushing disease are unknown, and pasireotide predisposes to hyperglycemia development (11). Clinical trials of retinoic acid in canine Cushing disease have shown promise, but have not been extended to human use (12).

EGFR activation, resulting either from mutation or from ligand or receptor overexpression, is associated with a variety of human cancers (13). EGF is a pituitary cell growth factor and also directly induces prolactin synthesis (14). Although approximately 60% of pituitary tumors — including ACTH-secreting adenomas (40%–80%) — express EGFR (15–18), the role of the receptor in tumorigenesis remains unclear. In pituitary corticotroph tumors expressing EGFR, $p27^{Kip1}$, a cyclin-dependent kinase inhibitor, is downregulated (18). Mice with disrupted p27 also develop pituitary tumors mostly expressing proopiomelanocortin (POMC), a precursor protein of ACTH (19–22). We hypothesized that the receptor could be a novel target for therapy of Cushing disease, and therefore tested EGFR signaling in ACTH-secreting pituitary adenomas.

Gefitinib, a tyrosine kinase inhibitor (TKI) targeting the EGFR, blocks activity at the intracellular ATP-binding site of the tyrosine kinase domain (23). Gefitinib exhibits efficacy in treating pulmonary adenocarcinoma, especially in female Asian nonsmokers with deletion mutants of exon 19 (del746_A750) or point mutations of exon 21 (L858R) (24). Gefitinib is also effective in other cancers that overexpress EGFR (either WT or mutants; refs. 25, 26).

Conflict of interest: The authors have declared that no conflict of interest exists.
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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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David S. Bruyette DVM

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Address correspondence to Dr. Lottati (Maya.Lottati@vca.com).

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

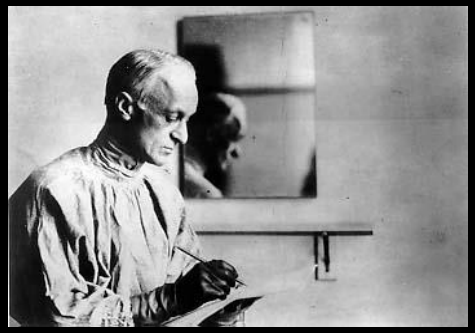
Pasireotide as administered in this study had no noted adverse effects on dogs with PDH and macroadenoma successfully managed with standard treatment. Placebo-controlled, randomized studies are needed to determine whether pasireotide protects from the development of neurologic signs or improves outcome 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.[1] 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.[2,3] 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.[2]

Two theories (hypothalamic and pituitary) have been proposed to explain the development of ACTH-producing pituitary tumors (corticotrophinomas).[4] The hypothalamic theory posits that the hypothalamus stimulates corticotrophs through enhanced secretion of corticotropin-releasing hormone and vasopressin.[5] 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.[6] A mutation in the glucocorticoid receptor gene results in a reduction in the number of DNA-binding sites while maintaining an affinity for cortisol.[7,8] This de novo mutation promotes a general resistance to glucocorticoids that precedes the formation of the corticotrophinoma. Studies[9,10] involving

ABBREVIATIONS

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



Acknowledgements:

Harvey Cushing, MD

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