

SÍNDROME DE CUSHING

Parte I

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Projeto ALIVE 2ª edição (Agreeing Language In Vet Endocrinol)



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Article

Agreeing Language in Veterinary Endocrinology (ALIVE): Cushing's syndrome and hypoadrenocorticism – a modified Delphi-method-based system to create consensus definitions

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Definição de Síndrome de Cushing

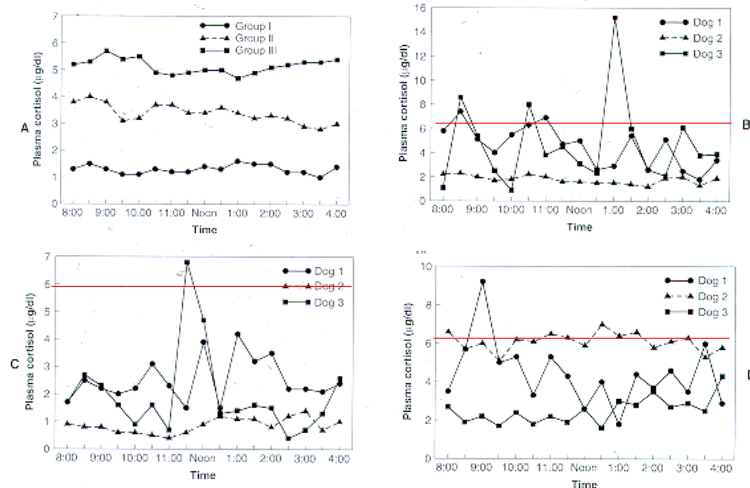
- Termo guarda-chuva para a variedade de síndromes clínicas causadas por atividade crônica de glicocorticoides, que podem ser causadas por diversos hormônios esteroides endógenos ou exógenos

ALIVE reconhece que a demonstração de um hipercortisolismo nem sempre está associado, e nem sempre causa síndrome de Cushing!

Da mesma forma, hipercortisolemia e síndrome de Cushing não necessariamente coexistem

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•Cortisol Basal (0,5-6 µg/dL) não tem valor diagnóstico



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DOENÇA DE CUSHING x SÍNDROME DE CUSHING

□ 1909-1912 Harvey Cushing faz os primeiros relatos de pacientes com HPD, publicação dos casos em 1932

□ Doença de Cushing → Termo restrito aos casos de hipercortisolismo resultantes de tumores hipofisários

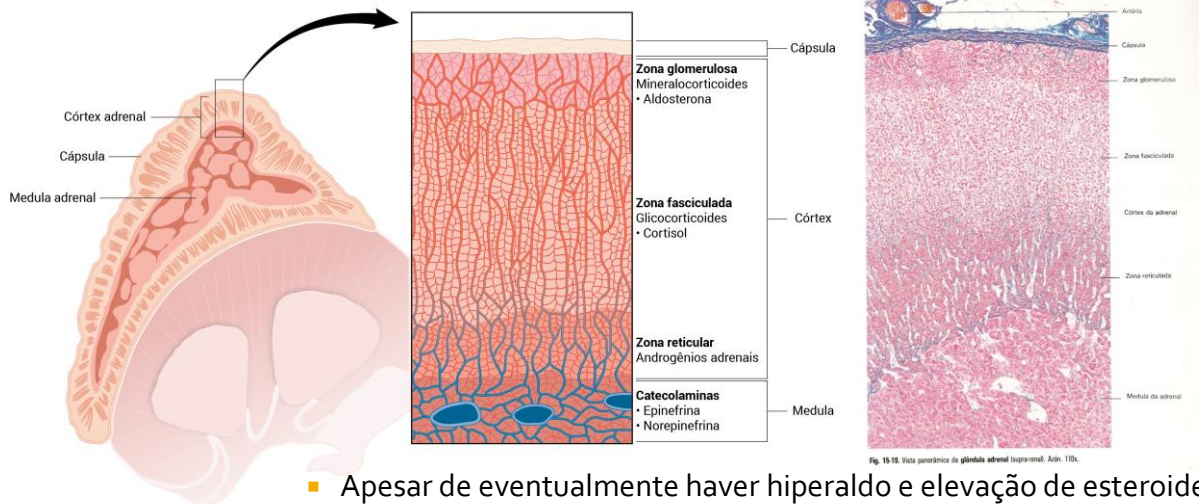
□ ALIVE não recomenda o uso do termo “Doença de Cushing” como sinônimo de “Síndrome de Cushing”

□ ALIVE desencoraja o uso do termo **HIPERADRENOCORTICISMO** para descrever a síndrome de Cushing!



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Pq Não usar o termo HAC?



- Apesar de eventualmente haver hiperaldo e elevação de esteroides sexuais, **Síndrome de Cushing refere à efeitos de GC**

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Efeitos Metabólicos dos Glicocorticoides

- Estímulo a gliconeogênese e antagonismo as ações da insulina
- Lipólise periférica, acúmulo gordura intra-abdominal
- Proteólise (substratos para gliconeogênese)
- Imunossupressão

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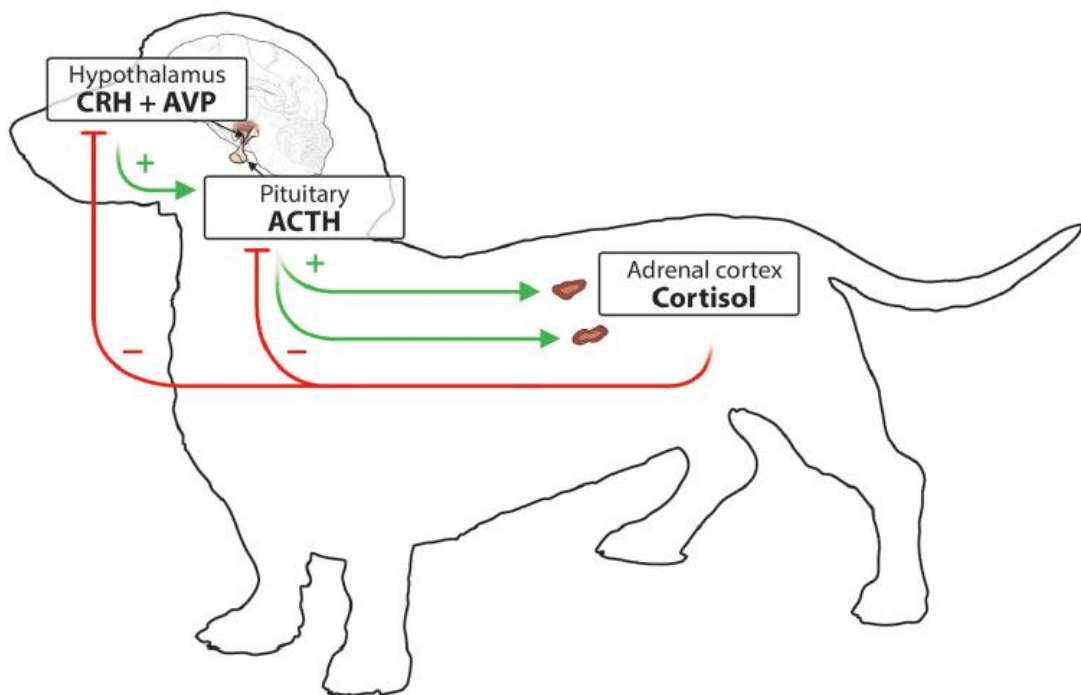
HIPERCORTISOLISMO

Excesso de atividade glicocorticoide secundário ao cortisol

- Polifagia
- Poliúria/Polidipsia
(principal causa em cães, pode ser o único sinal)
- Intolerância à exercícios
- Ofegação/taquipneia
- Hipogonadismo
- Atrofia e fraqueza muscular
- Aumento abdominal
- Rarefação pilosa bilateral simétrica
- Atrofia dérmica/telangiectasia
- Imunossupressão



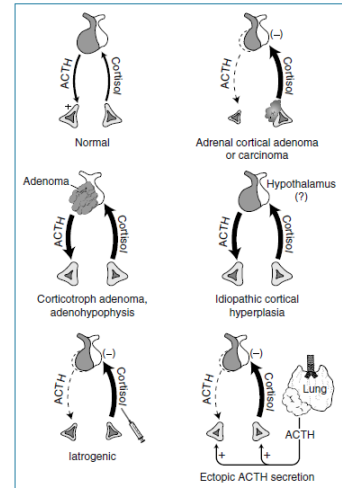
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Classificação Síndrome de Cushing (ALIVE)

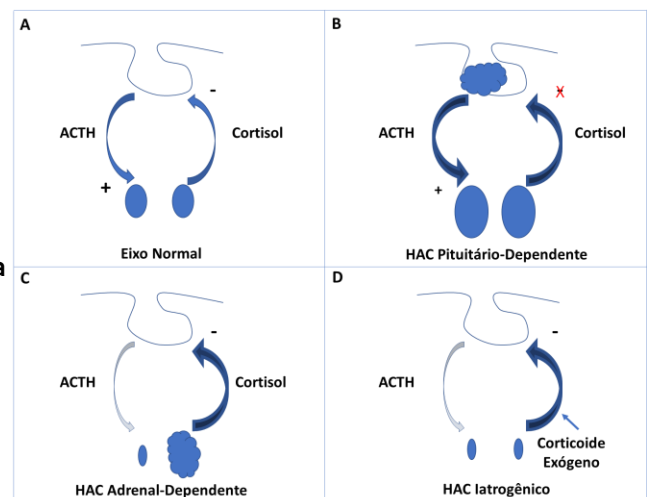
- **Ocorrência natural ACTH-Dependente**
 - Hiperkortisolismo Pituitário-Dependente (HPD)
 - Síndrome ACTH ectópico
 - SC Subdiagnosticada (atípico)
- **Ocorrência natural ACTH-Independente**
 - Hiperkortisolismo Adrenal-Dependente (HAD)
 - Receptores adrenais aberrantes (GIP, LH)
 - SC Subdiagnosticada (atípico)
- **Iatrogênica**



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Causas mais comuns na rotina

- **HPD = Hiperkortisolismo Pituitário-Dependente:** secreção autônoma e excessiva de ACTH com hiperplasia adrenocortical secundária (80-85% dos casos)
- **HAD = Hiperkortisolismo Adrenal-Dependente:** secreção autônoma excessiva de cortisol por adenomas ou carcinomas adrenocorticais (15-20% dos casos)
- **SC iatrogênica:** administração prolongada de glicocorticoides

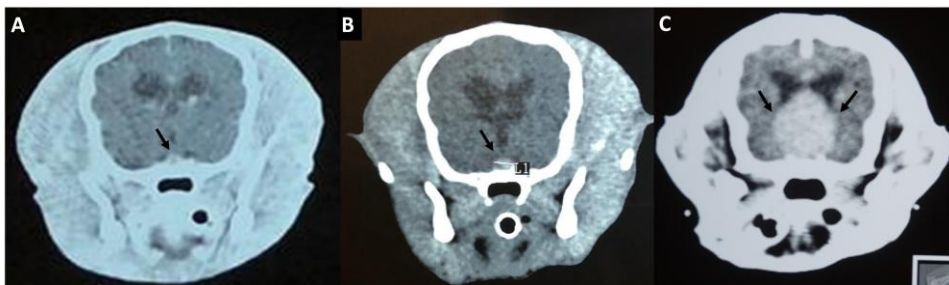


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HPD

Hipercortisolismo Pituitário-Dependente

- **Microadenomas:** cerca de 80% dos casos, tumores <1-10 mm, sendo normalmente menos de 3mm de diâmetro;
- **Macroadenomas:** cerca de 10 a 20% dos casos com tumores maiores que 1 cm e facilmente visualizados ao exame macroscópico



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HAD

Hipercortisolismo Adrenal-Dependente

Cerca de 50% deles Calcificam

- **Adenomas:** encapsulados, homogêneos com presença histológica de hematopoiese, trombos de fibrina, vacuolização citoplasma e Ki-67 < 2,4%
- **Carcinomas:** Tendem a ser invasivos localmente, > 2 cm diâmetro, heterogêneos e irregulares com presença histológica de fibrose periférica c/ ou s/ invasão capsular, crescimento trabecular, hemorragia, necrose
- Ki-67 > 2,4%



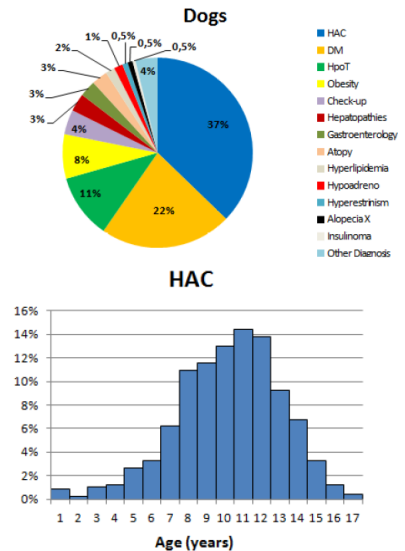
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Epidemiologia

- Uma das principais doenças de cães idosos, e a doença endócrina mais prevalente em cães!
- Doença de cães de meia idade à idosos > 6 anos
- Fêmeas castradas > risco
- Dados HCV:
 - Prevalência de 1:800 (0,125%) → 2026 ~1,5%
 - Idade média ~ 9 a 10 anos de idade
- **Ocorre em qualquer raça, mestiço ou SRD, e qualquer idade!**

Frequency of Endocrinopathies and Characteristics of Affected Dogs and Cats in Southern Brazil (2004-2014)

Alan Gomes Pöppel¹, Isadora Comparsi Coelho², Camila Alves da Silveira³, Mauricio Bianchini Moresco³, Guilherme Luiz Carvalho de Carvalho³



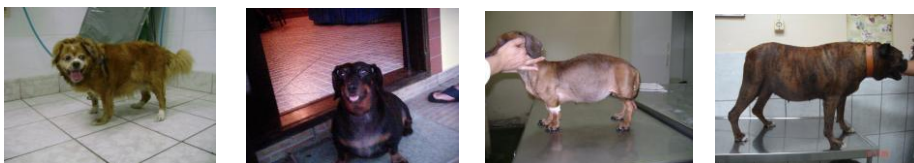
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A.G. Pöppel, I.C. Coelho, C.A. Silveira, M.B. Moresco & G.L.C. Carvalho. 2016. Frequency of Endocrinopathies and Characteristics of Affected Dogs and Cats in Southern Brazil (2004-2014). *Acta Scientiae Veterinariae*, 44: 1379.

Table 1. Frequency of breed distribution of dogs diagnosed with hyperadrenocorticism at the Division of Endocrinology between 2004 and 2014.

Breed	N	(%)
Poodle	181	34.7
Mixed breed	96	18.4
Dachshund	62	11.9
Yorkshire Terrier	40	7.7
Bichon Frise, Doberman Pinscher	17 (each)	3.3
Maltese	15	2.9
Beagle	14	2.7
Schnauzer	10	1.9
Shih Tzu	9	1.7
Labrador Retriever, Lhasa Apso	7 (each)	1.3
Boxer, Cocker Spaniel	6 (each)	1.1
Scottish Terrier	4	0.8
Chow-Chow, Fox Terrier	3 (each)	0.6
American Pit Bull Terrier, American Staffordshire Terrier, Border Collie, Chihuahua, German Shepherd Dog, German Spitz, Rottweiler, West Highland White Terrier,	2 (each)	0.4
Akita, Australian Shepherd Dog, Boston Terrier, Dogo Argentino, Fila Brasileiro, French Bulldog, Golden Retriever, Pekinese, Pug, Weimaraner	1 (each)	0.2
Total	522	100

- PDH mais comum em cães com menos de 20kg enquanto HAD mais comum em cães com mais de 20kg. **Porém os Shi tzus e Lhasas...**



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Histórico

- Curso da doença é lento e insidioso;
- Proprietários não percebem a doença;
- Acreditam que sinais são simplesmente decorrentes do envelhecimento do animal;
- Poucos pacientes apresentam todos os sinais clínicos, pode haver um único sinal predominante;
- Os sinais clínicos são a melhor ferramenta de triagem para Hiperadrenocorticismismo.



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MANIFESTAÇÕES CLÍNICAS DO HC

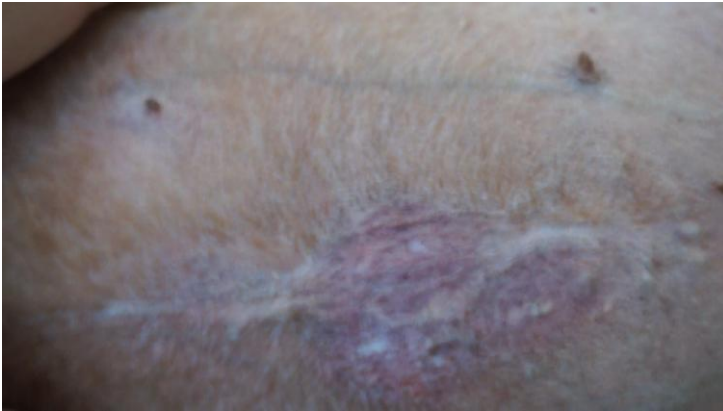
Diagnosis of Spontaneous Canine Hyperadrenocorticism: 2012
ACVIM Consensus Statement (Small Animal)

E.N. Behrend, H.S. Kooistra, R. Nelson, C.E. Reusch, and J.C. Scott-Moncrieff

COMUNS	MENOS COMUNS	INCOMUNS
PU/PD	Letargia	Tromboembolismo
Polifagia	Hiperpigmentação	Ruptura ligamentos
Ofegação	Comedões	Paralisia nervo facial
Abdômen abaulado	Pele fina	Pseudomiotonia
Hepatomegalia	Recrescimento piloso fraco	Atrofia testicular
Alopecia Endócrina	Incontinência urinária	Anestro persistente
Fraqueza muscular	Diabetes mellitus	
Hipertensão arterial		

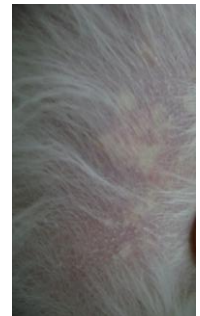
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Entrada pela dermatologia...



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Atrofia dérmica, Telangiectasia, Comedões, Piodermites, Calcinose cutis



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Fraqueza Muscular, Ruptura Ligamentos, Luxação Patela – Entrada pela Ortopedia



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Miotonia (Pseudomiotonia)



Received: 7 February 2022 | Accepted: 14 December 2022
DOI: 10.1111/jvim.16620

STANDARD ARTICLE

Journal of Veterinary Internal Medicine **ACVIM**
Open Access American College of Veterinary Internal Medicine

Clinical features of muscle stiffness in 37 dogs with concurrent naturally occurring hypercortisolism

Stefania Golinelli¹ | Federico Fracassi¹ | Ezio Bianchi² |
Álan Gomes Pöpl³ | Diego Daniel Miceli⁴ | Leontine Benedicenti⁵ |
Viviani De Marco⁶ | Audrey K. Cook⁷ | Laura Espada Castro⁸ |
Ian Ramsey⁸ | Kyoung Won Seo⁹ | Carlo Cantile¹⁰ | Gualtiero Gandini¹ |
Sean E. Hulsebosch¹¹ | Edward C. Feldman¹¹

¹Department of Veterinary Medical Sciences, University of Bologna, Bologna, Italy

²Department of Veterinary Medical Sciences, University of Parma, Parma, Italy

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⁴Endocrinology Unit, School of Veterinary Medicine, University of Buenos Aires, Faculty of Veterinary Sciences, Buenos Aires, Argentina

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⁶New Especialidades, São Paulo, Brazil

⁷Department of Small Animal Clinical Sciences, College of Veterinary Medicine and Biomedical Sciences, Texas A&M University, College Station, Texas, USA

⁸School of Veterinary Medicine, University of Glasgow, Glasgow, UK

⁹Department of Veterinary Internal Medicine, College of Veterinary Medicine, Seoul National University, Seoul, South Korea

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¹¹Department of Medicine and Epidemiology, School of Veterinary Medicine, University of California, Davis, California, USA

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Taquipneia / Dispneia / Cianose / Abaulamento Abdominal – Entrada pela Cardiologia



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Hipertensão arterial sistêmica

Received: 29 December 2019 | Accepted: 13 June 2020
DOI: 10.1111/jvim.15841

STANDARD ARTICLE

Journal of Veterinary Internal Medicine ACVIM
Official Journal of the American College of Veterinary Internal Medicine

Prevalence and risk factors associated with systemic hypertension in dogs with spontaneous hyperadrenocorticism

Paula García San José¹ | Carolina Arenas Bermejo² | Irene Clares Moral³ |
Pedro Cuesta Alvaro⁴ | María Dolores Pérez Alenza¹

Background: Systemic hypertension (SH) is common in dogs with hyperadrenocorticism (HAC) however there are not many studies assessing its prevalence and risk factors.

Objectives: To determine the prevalence and severity of SH in dogs with HAC and its association with clinical and laboratory findings to identify potential risk factors.

Animals: Sixty-six client owned dogs with spontaneous HAC.

Methods: Retrospective cross-sectional study. Medical records of dogs with HAC were reviewed. Systolic blood pressure (SBP) was measured using Doppler ultrasonography. Clinical signs, physical examination findings and clinicopathologic data (CBC, serum biochemistry and electrolytes, urinalysis and urinary culture, and adrenal function tests) were reviewed for analysis.

Results: Prevalence of SH (≥ 150 mm Hg) was 82% (54/66) and prevalence of severe SH (≥ 180 mm Hg) was 46% (30/66). All dogs with thrombocytosis had SH ($P = .002$), and a platelet count $\geq 438 \times 10^3/\mu\text{L}$ was 100% specific and 61.1% sensitive to predict SH (AUC = .802, $P = .001$). Median potassium levels were lower in hypertensive dogs (4.1 mEq/L, range 3.1–5.4 mEq/L) than in normotensive ones (4.5 mEq/L, range 4.0–5.0 mEq/L) ($P = .007$). Dogs with UPC ≥ 0.5 had higher median SBP than those without proteinuria ($P = .03$). Dogs with concurrent diabetes mellitus seemed to have a reduced risk of SH (OR = .118, 95%CI = .022–.626, $P = .02$).

Conclusions and Clinical Importance: Systemic hypertension is common in dogs with HAC and is frequently severe. Blood pressure should be routinely assessed in these dogs, especially if thrombocytosis, proteinuria or low potassium concentrations are present.

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Sinais Neurológicos Centrais, Neuropatias periféricas – Entrada pela Neurologia

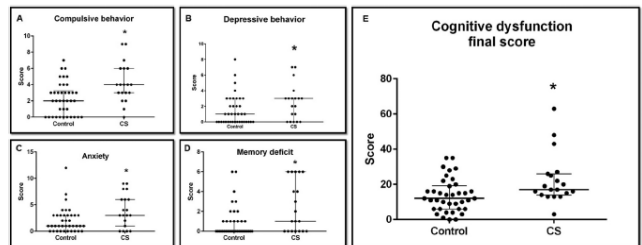


Short Communication

Cognitive dysfunction severity evaluation in dogs with naturally-occurring Cushing's syndrome: A matched case-control study

Check for updates

Carolina Castilhos da Silva^a, Ingrid Cavalcante^b, Guilherme Luiz Carvalho de Carvalho^c, Alan Gomes Pöppel^{a,c,d}



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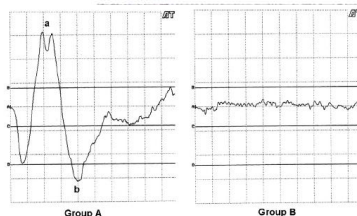
Alterações Oculares - Entrada pela Oftalmo

- Exoftalmia,
- Úlceras indolentes,
- Ceratite p/ dep. Triglicérido
- Degeneração de retina (SARD?)
- Cegueira



Blindness in dogs with pituitary dependent hyperadrenocorticism: Relationship with glucose, cortisol and triglyceride concentration and with ophthalmic blood flow

M.F. Calhaz-Batista^a, A. del Prado^b, M.F. Galvão^c, S. Pimenta^d, J. Nunes^e, M. Evans^f, B.D. Mitchell^g, N.C. Gilman^h, V.A. Castelhóⁱ



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Assessment of Coagulation and Potential Biochemical Markers for Hypercoagulability in Canine Hyperadrenocorticism

S.L. Pace, K.E. Creevy, P.M. Krimer, and B.M. Brainard

Background: Anecdotal accounts and limited research suggest that dogs with spontaneous hyperadrenocorticism (HAC) are at risk of developing thromboembolic complications. Detailed description of coagulation status and identification of subsets of dogs at greatest risk would impact therapeutic recommendations for these patients.

Hypothesis/Objectives: *Hypothesis:* A subset of dogs with HAC will have a hypercoagulable tendency as identified by increased procoagulant activity, decreased fibrinolysis, or both. *Objective 1:* To document the existence of this hypercoagulable tendency in HAC dogs using assays of individual coagulation factors, fibrinolytic activity, and systemic coagulation. *Objective 2:* To evaluate clinical and biochemical markers in HAC dogs to identify a subset of HAC patients at increased risk of this hypercoagulable tendency.

Animals: Seventeen dogs newly diagnosed with HAC.

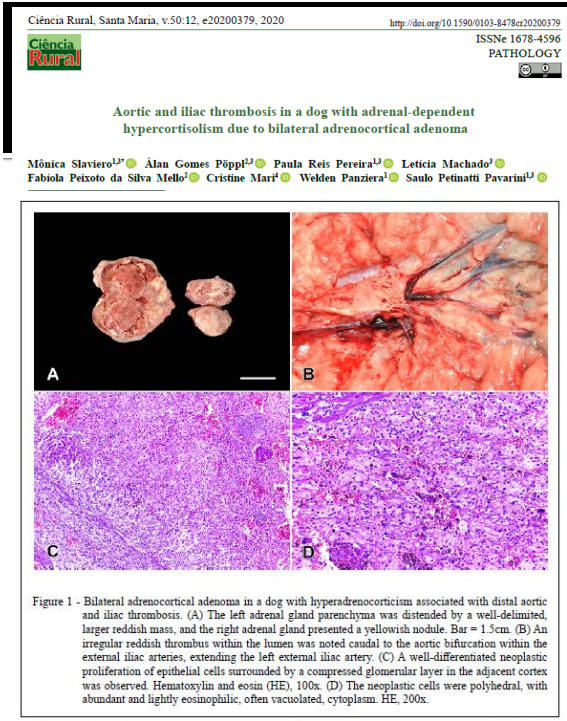
Methods: Prospective study. Medical history, physical examination findings, routine diagnostic tests, and comprehensive coagulation testing were performed at the time of HAC diagnosis. Coagulation parameters were assessed individually and as panels for each dog. Historical and clinical variables were correlated with coagulation parameters to identify risk factors.

Results: The majority (88.2%) of HAC dogs exhibited a hypercoagulable tendency. Abnormalities in 1 coagulation assay did not predict abnormalities in others. Duration of clinical signs of HAC did not predict hypercoagulability. Comorbid conditions or abnormal clinicopathologic parameters that predicted hypercoagulability were not identified.

Conclusions and Clinical Importance: Although HAC dogs may demonstrate a hypercoagulable tendency individually and as a group, comorbid conditions or biochemical variables that would predict more severe coagulation abnormalities were not identified.

Key words: Cushing's disease; Dog; Fibrinolysis; TEG; Thromboembolism.

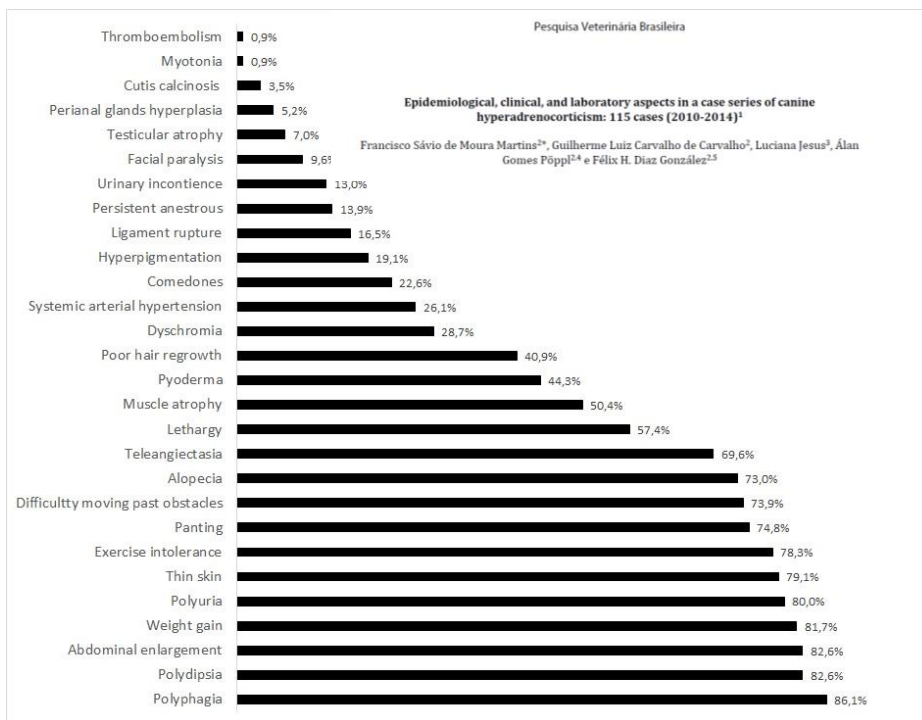
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Trombose e Tromboembolismo





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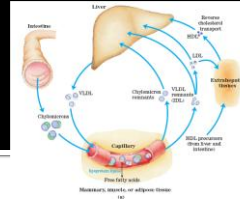
Patologia Clínica no Hiper cortisolismo

- Importante fator preditivo de HAC frente a suspeita clínica
- Auxiliam na compreensão do grau de comorbidades associadas à doença
- Auxiliam no monitoramento do tratamento
- Eventualmente achados em exames de rotina motivam o início da investigação



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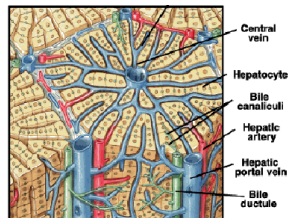
Patologia Clínica no Hiper cortisolismo



- Eritrocitose, macrocitose
- Anemia em casos crônicos (~10-15%)
- **Leucograma de estresse** (neutrofilia, monocitose, linfopenia e eosinopenia - **80% casos**)
- Trombocitose (> 500.000/mm³)
- Redução TP e TTPA

■ FA (N, ↑, ↑↑, ↑↑↑) 80-95% dos casos

- GGT (N, ↑)
- ALT (N, ↑)
- Creat
- Fósforo } (N, ↓)
- Ureia



- Glicemia (N, ↑, ↑↑)
- Triglicerídeos (N, ↑, ↑↑, ↑↑↑)
- Colesterol (N, ↑, ↑↑)

■ EQU:

- **DEU:** 1.001 a > 1.030 (**<1.020**)
- RP:CU (N, ↑, ↑↑)
- Proteinúria glomerular x tubular
- Bacteriúria subclínica - <15%
- Tendência cristalúria e cálculos OxCa

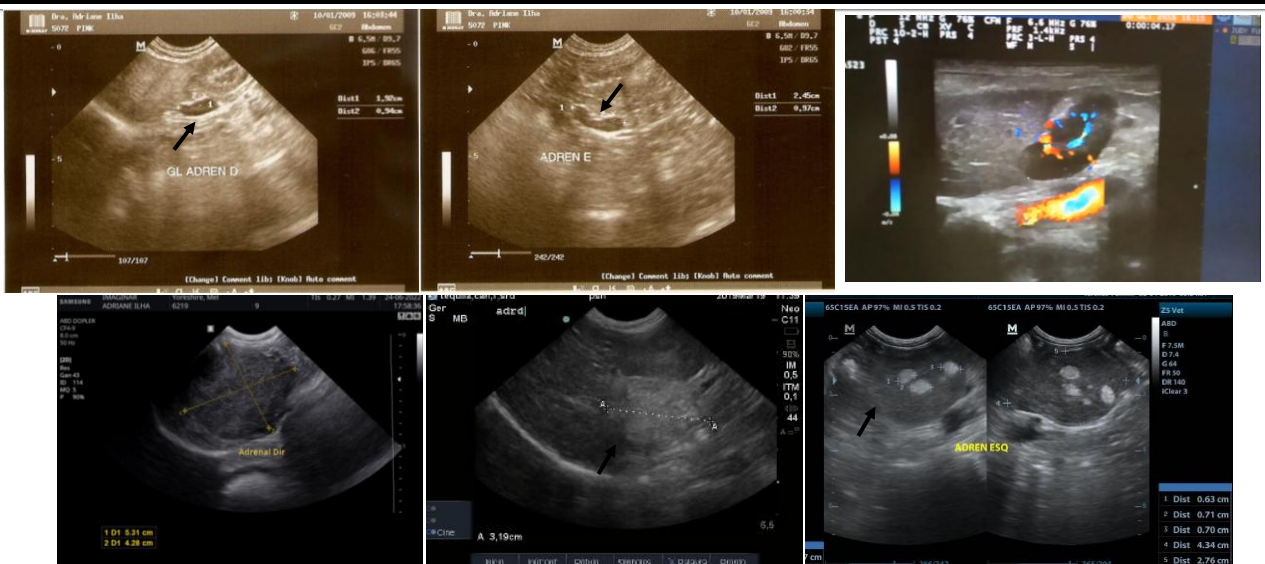


Clinical and microbiological characterization of subclinical bacteriuria and sporadic bacterial cystitis in dogs with spontaneous hypercortisolism

Leticia Machado^a, Milena Claff de Oliveira^a, Cláudia Regina Barbieri^b, Camila Império Riboldi^b, Vanessa Bielefeldt Leoni^c, Félix Hilário Dias Gonçalves^{a,c}, Stella de Faria Valle^{a,c}, Franciele Maltoni Siqueira^{a,c}, Alan Gomes Pöppel^{a,c}

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Avaliação Morfológica das Adrenais na Ultrassonografia



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Pontos de corte para caracterizar hiperplasia

- >2,5-5 kg = 5.1 mm
- >5-10 kg = 5.5 mm
- >10-20 kg = 7.5 mm
- >20-40 kg = 8.7 mm
- Sens. Hiperplasia 95,6%
- US classificou 56% casos como HPD ou HAD, porém 39,6% com assimetria equívoca
- Atrofia < 5 mm ? Depende do peso...

Received: 28 March 2020 | Revised: 1 December 2020 | Accepted: 26 February 2021, e80.
DOI: 10.1002/vet.380

ORIGINAL RESEARCH

VetRecord

Ultrasound evaluation of adrenal gland size in clinically healthy dogs and in dogs with hyperadrenocorticism

Carlos Mellán^{1,2} | Laura Pérez-López² | Pedro Saavedra³ |
Antonio G. Ravelo-García⁴ | Yaiza Santos¹ | José Raduan Jaber⁵

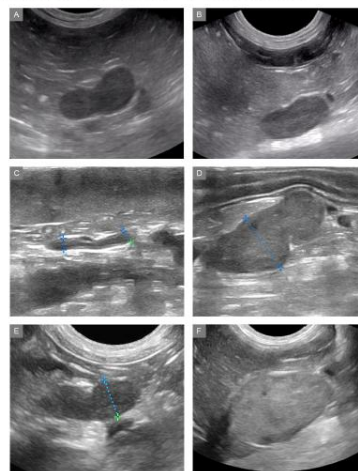
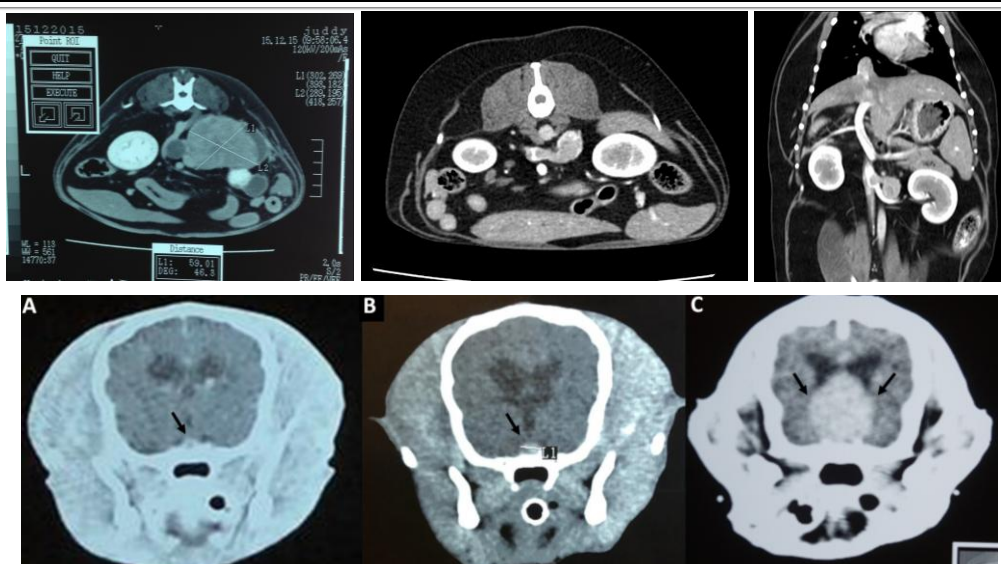


FIGURE 1 Adrenal gland ultrasound images of dogs with hyperadrenocorticism, consistent with PHD, EAA, or EAA. Left (A) and right (B) adrenal glands of a 4 kg dog with symmetrical enlargement of both adrenal glands consistent with PHD. The MTL and MTR were 10.1 and 10 mm, respectively. Left (C) and right (D) adrenal glands of a 10 kg dog with unilateral adrenomegaly and contralateral adrenal gland atrophy consistent with EAA. The MTL and MTR were 2.9 and 12.7 mm, respectively. Left (E) and right (F) adrenal glands of a 7.2 kg dog with asymmetrical bilateral adrenomegaly. The MTL and MTR were 8.1 and 20.5 mm, respectively

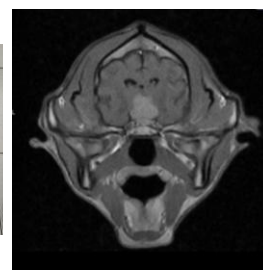
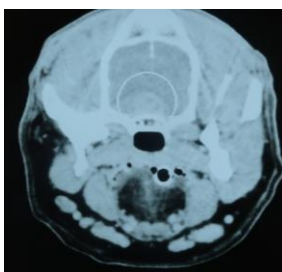
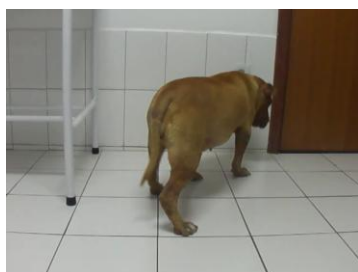
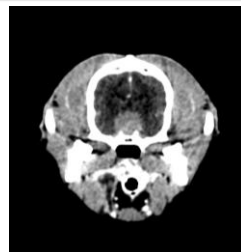
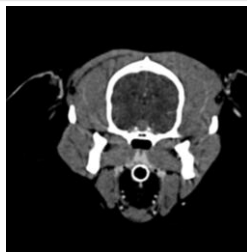
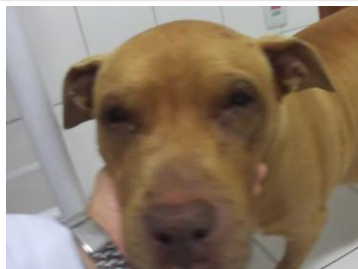
33

Imagens Avançadas (TC, RM)



34

Imagens Avançadas (TC, RM)



35

TESTES HORMONAIS NO HC

❖ Teste de triagem

- Relação cortisol:creatinina urinária (RC:CU)

❖ Testes de diagnóstico (Dinâmicos)

- Teste de supressão por baixa dose de dexametasona (TSpBDD)
- Cortisol sérico ou urinário
- Teste de estimulação por ACTH (TEpA)

❖ Testes de diferenciação origem (HPD x HAD)

- TSpBDD
- TSpADD
- ACTH endógeno
- Imagens adrenais e de hipófise



36

Quem deve ser Testado?

- ❖ Presença de 1 ou mais dos sinais clínicos clássicos, ou achados do exame físico,
- ❖ Quanto mais alterações forem reconhecidas, mais forte a indicação para teste, especialmente as manifestações menos comuns
- ❖ Falha em reconhecer múltiplas manifestações NÃO Descarta o HC
- ❖ Os achados laboratoriais NÃO SÃO patognomônicos, e a ausência deles não descarta o HC
- ❖ Resultados de patologia clínica, RPCU e de PAS devem ser interpretados à luz da história clínica do paciente,
- ❖ Ausência de manifestações clínicas e laboratoriais compatíveis é um fator preditivo negativo forte para HC,
- ❖ Identificação de alterações em imagens de adrenais (neoplasia, hiperplasia) ou hipófise
- ❖ Diabéticos com fraco controle...



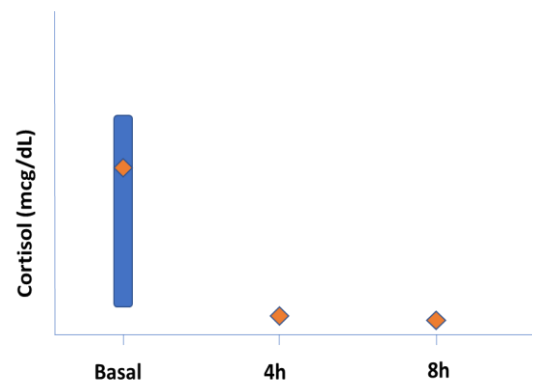
37

Teste de Supressão por Baixa Dose Dexametasona

Avalia a sensibilidade do Eixo HHA à supressão por glicocorticoides - contínua e não tudo ou nada!

1. Coleta amostra basal
2. Aplicação 0,01-0,015 mg/kg dexametasona IV
 - Em gatos dose é 0,1 mg/kg IV
3. Coletas pós 4 e 8h pós-dexa

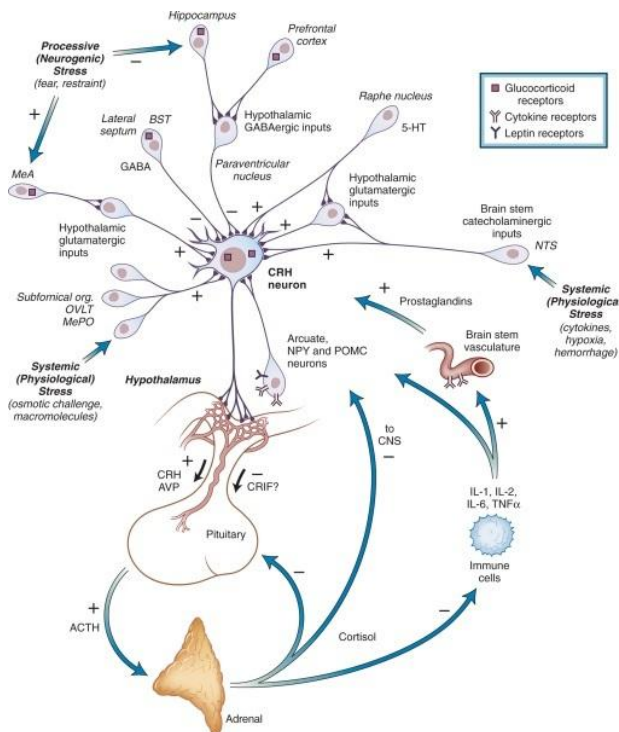
SENSIBILIDADE – 85 a 100%
ESPECIFICIDADE – 44 a 73%



38



38



Eixo Corticotrófico

- ✓ **CRH**
- ✓ Controle produção de ACTH pelos corticotrofos
- ✓ Regulação:
 - ✓ Feedback negativo GCs sobre CRH e ADH
 - ✓ Controle neural (alça feedback aberta):
 - ✓ Estressores neurogênicos
 - ✓ medo, contenção, dor, jejum → ↑CRH
 - ✓ Estressores fisiológicos
 - ✓ Osmólitos, hemorragia → ↑ADH
 - ✓ Citocinas, hipóxia, hipoglicemia → ↑CRH

Obs: Mesmo na presença de excesso de GCs, supressão ACTH pode ser revertida frente a estressor adicional (↑CRH)

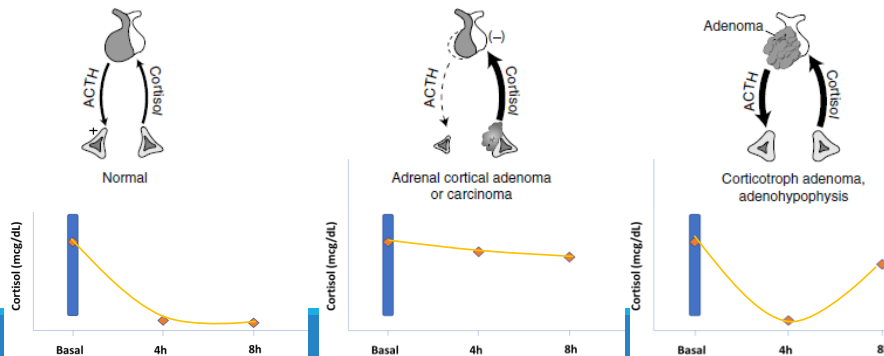
39



Interpretação TSpBDD:

1. + para Cushing? → Cortisol 8h pós-dexa
2. HPD ou HAD? → Relação cortisol 4h x basal

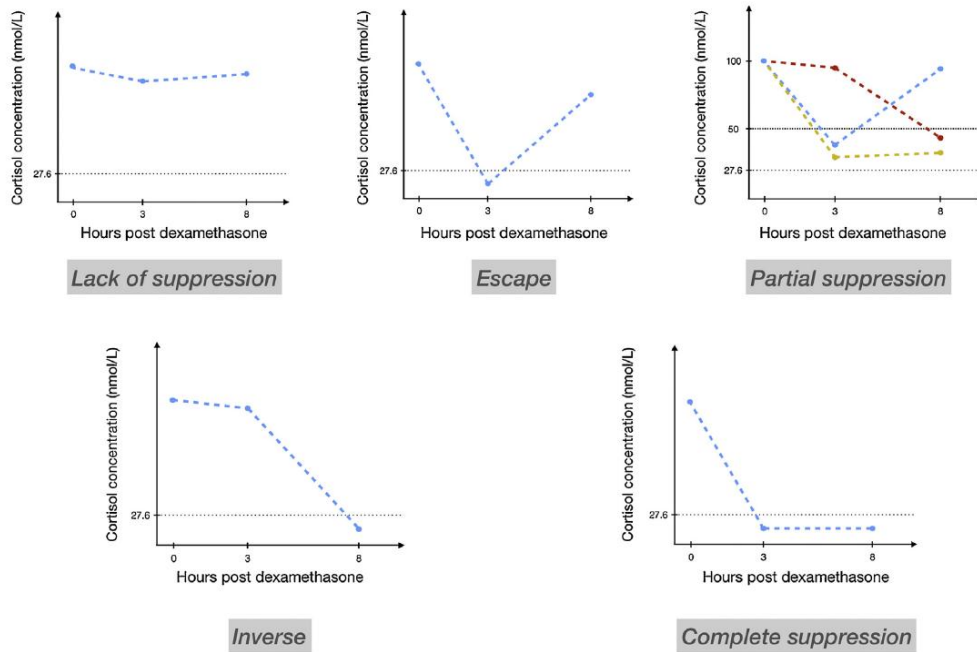
1. Normal - Supressão completa (4 e 8h < 1 mcg/dl)
2. HAD - Falta de supressão (4 e 8h > 1 mcg/dl, e > 50% t0)
3. HPD - Padrão de Escape (4h < 1, e 8h > 1 mcg/dl), Supressão Parcial ou Falta de Supressão



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M. Bennaim et al./The Veterinary Journal 252 (2019) 105343

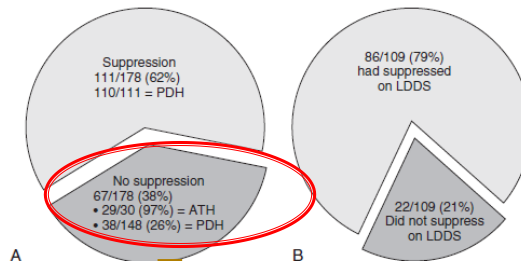


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"Supress or not supress"

- Pacientes que não suprimem podem ser PDH ou TAF
- Pacientes que suprimem são pituitário-dependentes

FIGURE 10-30 A. Of 178 dogs with naturally occurring hyperadrenocorticism (HAC) that were tested with both the low-dose and high-dose dexamethasone suppression tests (LDDST and HDDST), 111 dogs suppressed using one of the criteria defined in the text. Of the 111 dogs, 110 had pituitary-dependent hyperadrenocorticism (PDH). Twenty-nine of 30 dogs (97%) with adrenal tumors did not suppress using any of the criteria, and 38 of the 148 dogs with PDH (26%) did not suppress. **B.** Of the 109 dogs that suppressed on the HDDST, 86 (79%) had already shown suppression on the LDDST.



TSADD?
Exames de Imagem
ACTH endógeno

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Received: 25 September 2017 | Revised: 5 January 2018 | Accepted: 23 January 2018
DOI: 10.1111/jvim.15079

STANDARD ARTICLE

Background: Dogs with hyperadrenocorticism (HAC) may be more mildly affected at the time of diagnosis today, which could influence the prevalence of associated clinical and clinicopathological abnormalities and diagnostic test performance. Different low-dose dexamethasone suppression test (LDDST) result patterns have not been evaluated individually.

Objectives: To assess the current features of HAC and evaluate if the diagnostic test performance of individual LDDST result patterns differ.

Animals: One hundred and twenty-three dogs undergoing investigation for HAC.

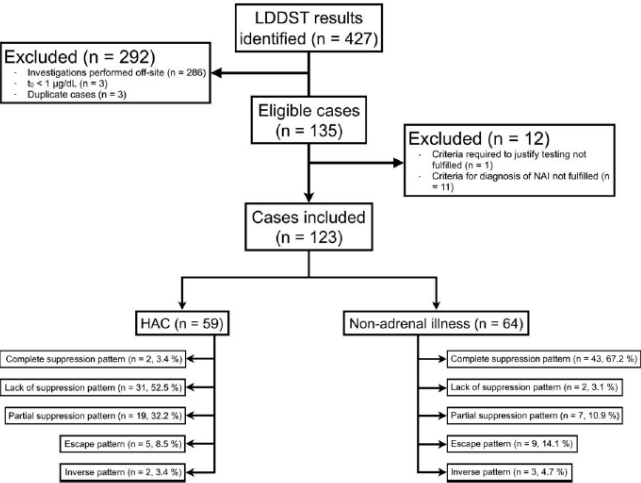
Methods: Retrospective evaluation of dogs in which a LDDST was performed and HAC confirmed or excluded by alternative means. Cases with basal cortisol concentrations ($t_0 < 1 \mu\text{g/dL}$) were excluded. Each LDDST result was classified as (a) complete suppression (t_3 and $t_8 < 1 \mu\text{g/dL}$), (b) lack of suppression (t_3 and $t_8 > 1 \mu\text{g/dL}$ and both $> 50\%$ t_0), (c) partial suppression (t_3 and $t_8 > 1 \mu\text{g/dL}$ but either $< 50\%$ t_0), (d) escape ($t_8 > 1 \mu\text{g/dL}$ and $t_3 < 1 \mu\text{g/dL}$) or (e) inverse ($t_3 > 1 \mu\text{g/dL}$ and $t_8 < 1 \mu\text{g/dL}$) pattern.

Results: Fifty-nine (48%) dogs were diagnosed with HAC and 64 (52%) with non-adrenal illness. Hyperadrenocorticism cases had similar clinicopathological abnormalities compared to previous reports. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) (95% confidence interval [CI]) of the LDDST for diagnosing HAC were 96.6 (91.9–100)%, 67.2 (55.7–78.7)%, 73.1 (63.2–82.9)%, and 95.6 (89.5–100)%, respectively. Lack of suppression pattern had the highest PPV (93.9 [85.8–100]%) followed by the partial suppression pattern (67.9 [50.6–85.2]%) and escape or inverse pattern (36.8 [15.1–58.5]%).

Conclusions and Clinical Importance: A lack of suppression LDDST pattern has the highest PPV for diagnosing HAC followed by a partial suppression pattern. By contrast, the escape or inverse pattern provided limited support of HAC.

Evaluation of individual low-dose dexamethasone suppression test patterns in naturally occurring hyperadrenocorticism in dogs

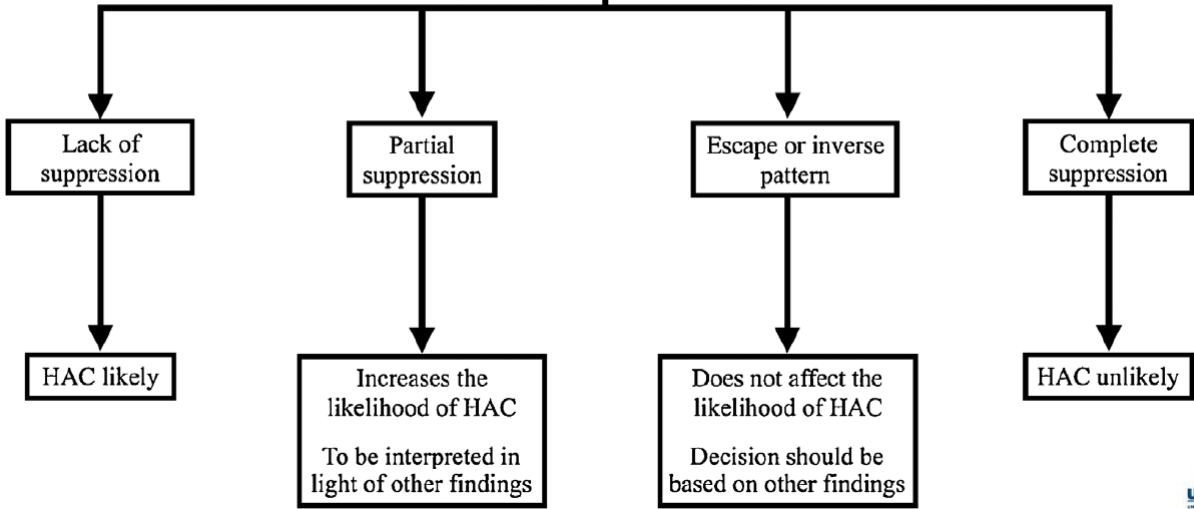
Michael Bennaim  | Robert E. Shiel | Christopher Forde | Carmel T. Mooney



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The Veterinary Journal 2018; 90:245
Contents lists available at ScienceDirect
The Veterinary Journal
journal homepage: www.elsevier.com/locate/jvet
Invited review
Diagnosis of spontaneous hyperadrenocorticism in dogs. Part 2: Adrenal function testing and differentiating tests
Michael Bennaim^a, Robert E. Shiel, Carmel T. Mooney
^aSection of Small Animal Clinical Studies, School of Veterinary Medicine, University College Dublin, Ireland

LDDST



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Qual seu ponto de corte para dizer SIM?

Qual ponto de corte seu lab usa?

- 8h pós-dexa > 2 mcg/dL?
- 8h pós-dexa > 1,4 mcg/dL?
- 8h pós-dexa > 0,8 mcg/dL?

De onde veio este valor?

Podemos transpor valores de referência da literatura?

Podemos comparar valores entre diferentes métodos?

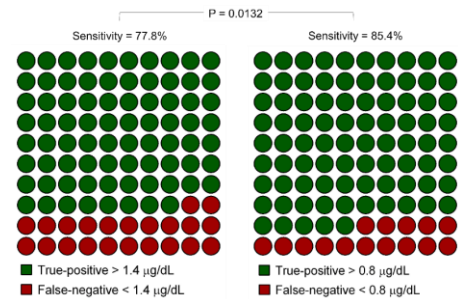
Mesmo método em diferentes Labs dão o mesmo resultado?

Arq. Bras. Med. Vet. Zootec.

A retrospective cohort study of 122 dogs treated for hypercortisolism: low-dose dexamethasone suppression test sensitivity and comparative outcomes in response to mitotane or trilostane

[Estudo de coorte retrospectivo de 122 cães que receberam tratamento para hipercolesterolemia: sensibilidade do teste de supressão por baixa dose de dexametazona e comparação entre os desfechos em relação ao mitotano ou ao trilostano]

M.M. Marçal¹, S.F.M. Martins², C.R. Barbieri³, T.B. Nogueira⁴, Á.G. Pöppl^{1,4}



45

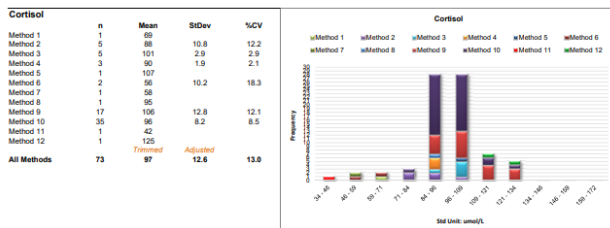
Programa de Avaliação Externa de Qualidade (EQA-ESVE)

ESVE Veterinary Endocrinology External Quality Assessment Scheme

ESVE REPORT

Release Month: May-19
Release Number: 014
Species: Canine

Analyte results



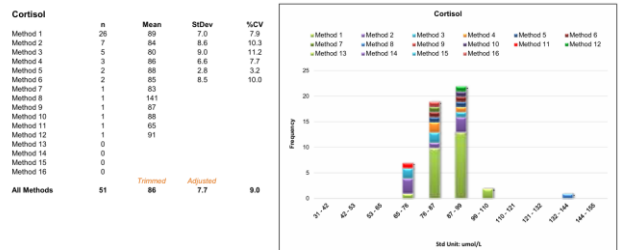
Note: Reported results ranged from 42 to 125nmol/L. Although Method 11 yielded a low result compared to the consensus, it is reported against a lower reference range than most other labs. Methods 7 & 8 were in-clinic analyzers.

ESVE Veterinary Endocrinology External Quality Assessment Scheme

ESVE REPORT

Release Month: May-23
Release Number: 018
Species: Canine

Analyte results



Note: Reported results ranged from 65 to 141nmol/L. Method 13 was an in-clinic analyzer. Method 1 is Immulite 2000 Veterinary Cortisol. Method 2 and 3 were Immulite 2000 non-vet Cortisol adj and unadj respectively.

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Teste de Estimulação por ACTH

Avalia a reserva adrenal

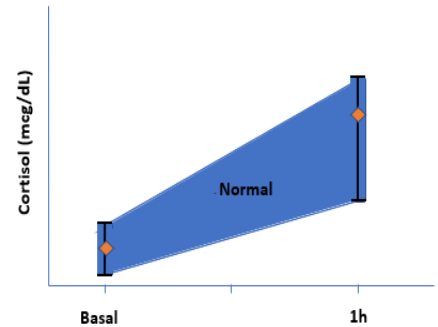


1. Coleta para cortisol basal
2. Aplicação 5 mcg/kg de cosyntropin (Cortrosyn), tetracosactide (Synacthen/**COSACTHEN**) ou ACTH suíno recombinante (ACTHEL), IV
 - GATOS usar 5 mcg/kg ou 125 mcg/gato
3. Coleta para cortisol pós-ACTH em 60 minutos

SENSIBILIDADE p/ HPD – 80 a 95%

SENSIBILIDADE p/ HAD – 57 a 63%

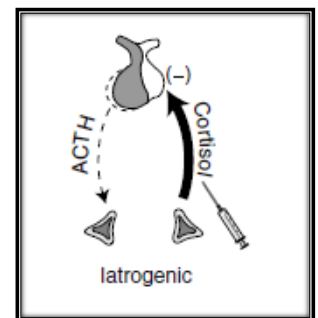
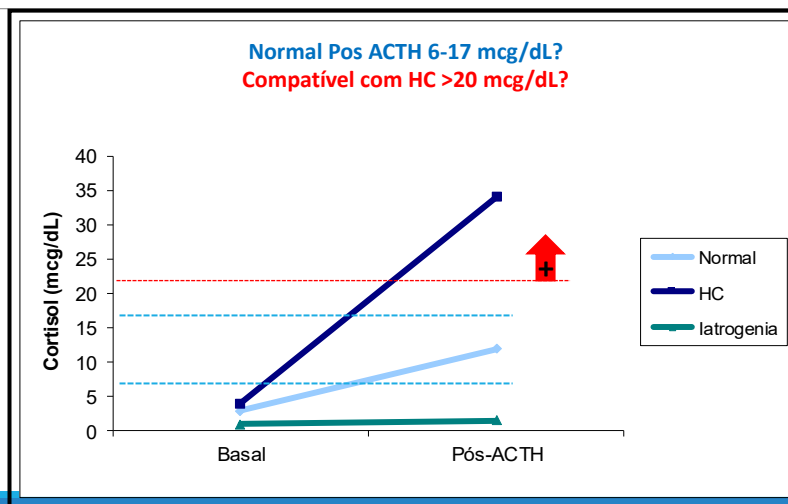
ESPECIFICIDADE – 59 a 93%



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Interpretação TEpACTH:

1. + para Cushing? → Cortisol pós-ACTH
2. Espontâneo ou Iatrogênico ?



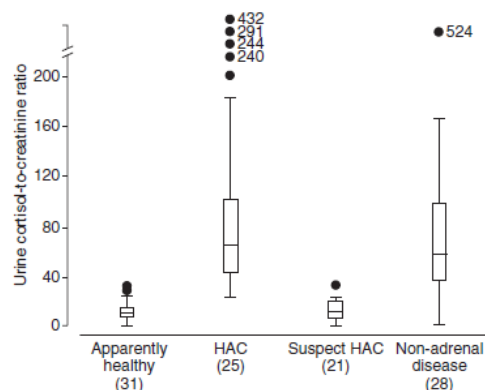
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Relação Cortisol:Creatinina Urinária (RC:CU)

Coleta dever ser realizada em casa, primeira urina da manhã

INTERPRETAÇÃO:

- Relação normal ➔ negativo para Cushing
- Relação alta ➔ Compatível com Cushing
 - Sensibilidade ➔ 92-100%
 - Especificidade ➔ ~21-24%
- ❖ Possibilidade de associar com TSADD, administrando dexam oral 0,1 mg/kg as 12h, 18h e 24h no 1º dia
 - Coleta urina pela manhã no 2º e 3º dia
 - **INTERPRETAÇÃO:**
 - Supressão < 50% HPD ou HAD
 - Supressão > 50% HPD



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AJVR



Urinary cortisol-to-creatinine ratio using a chemiluminescent assay has limited diagnostic accuracy for canine hypercortisolism

Francesca Del Baldo, VMD, PhD, DECVIM^{1*}; Alessandro Tirolo, VMD²; Francesco Dondi, VMD PhD¹; Ada Sapignoli, VMD¹; Matteo Galeotti, VMD¹; Antonio Maria Tardo, VMD¹; Stefania Golinelli, VMD, PhD¹; Federico Fracassi, VMD, PhD, DECVIM¹

- ❖ Sensibilidade 80,4%
- ❖ Especificidade 71,4%
- ❖ Immulite 2000 xpi

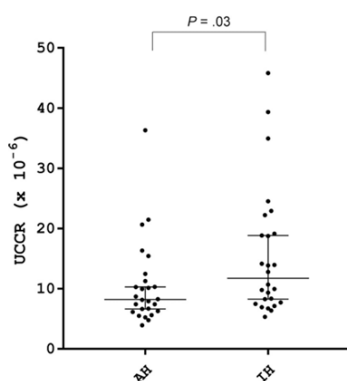
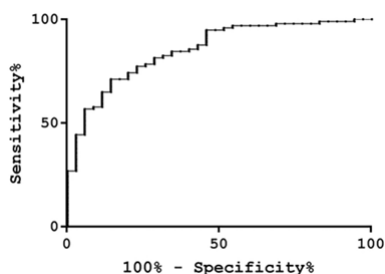


Figure 1—Scatter scale plot comparing urinary cortisol-to-creatinine ratio (UCCR) for urine samples collected in hospital (IH) and those collected at home (AH). The horizontal bars represent the median and the 95% CI.

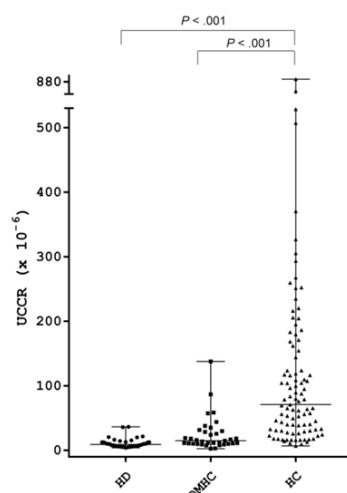
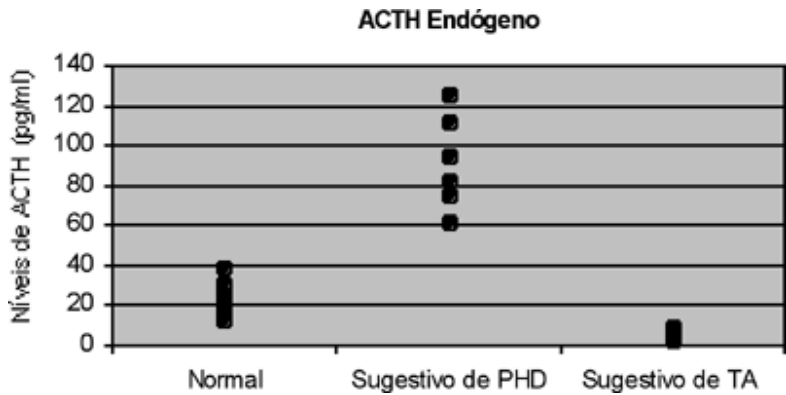


Figure 2—Scatter scale plot comparing UCCR of dogs with hypercortisolism (HC; n = 97), dogs with diseases mimicking HC (DMHC; n = 35), and healthy dogs (HDs; n = 40). The horizontal bars represent the median, the maximum, and the minimum value of each group.

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ACTH endógeno

- Coleta tubo EDTA pré-refrigerado
- Centrifugação imediata (preferência centrífuga refrigerada) 3 min
- Análise imediata ou congelamento e envio em gelo seco



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Envio de Amostras para Mensuração de ACTHe

Ciência Rural, Santa Maria, v.51:1, e20200282, 2020



<http://doi.org/10.1590/0103-8478cr20200282>

ISSN 1678-4596
CLINIC AND SURGERY

Canine endogenous adrenocorticotrophic hormone preanalytical stability after sample shipping in dry ice or recyclable ice bars

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Rogério Soila² Priscila Viua Furtado³

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²PROVET Medicina Veterinária Diagnóstica, Laboratório de Hormônios, São Paulo, SP, Brasil.
³Laboratório de Hormônios, Faculdade de Medicina Veterinária e Zootecnia, Universidade de São Paulo (USP), Butantã, SP, Brasil.

ABSTRACT: Endogenous adrenocorticotrophic hormone (eACTH) measurement is useful in hypercortisolism and hypoadrenocorticism investigation; however, since the hormone is highly unstable, blood samples require proper processing and storage, as well as shipping is often a step limiting since few laboratories offer this assay in Brazil. The aim of this note was to compare overnight dog's eACTH preanalytical stability when frozen samples were shipped in dry ice (DI), or with recyclable ice bars (RIB). A total of 56 paired samples for eACTH measurement were analyzed. Blood samples were properly handled, plasma aliquots transferred into plastic microtubes, and stored at -80°C. The fifty-six paired samples were overnight shipped in two thermic isolated boxes with DI or involved by RIB. Despite there was a high correlation between results from both shipping methods (r Spearman = 0.958, $P < 0.001$), the Wilcoxon matched-pairs rank test showed that the shipping method may influence results ($P < 0.001$). However, this difference does not affect results interpretation. By this way, when DI shipping was not possible, RIB shipping may represent a risk to eACTH preanalytical stability.

Key words: ACTH determination, shipping method, hyperadrenocorticism, hypercortisolism, hypoadrenocorticism.

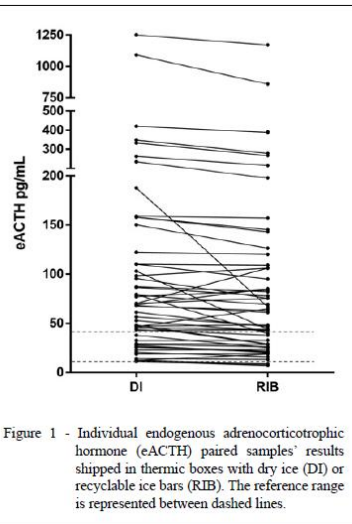


Figure 1 - Individual endogenous adrenocorticotrophic hormone (eACTH) paired samples' results shipped in thermic boxes with dry ice (DI) or recyclable ice bars (RIB). The reference range is represented between dashed lines.

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Article

Agreeing Language in Veterinary Endocrinology (ALIVE): Cushing's syndrome and hypoadrenocorticism – a modified Delphi-method-based system to create consensus definitions

Stijn J.M. Niessen^{1,2,3,4,*}, Ellen N. Behrend^{2,5}, Federico Fracassi⁶, David B. Church¹, Sue F. Foster⁷, Sara Galac⁸, Carlos Melian^{9,10}, Alan G. Pöppel^{11,12}, Ian K. Ramsey¹³, Nadja S. Sieber Ruckstuhl¹⁴, ESVE/SCE membership

Critérios ALIVE para diagnóstico de Síndrome de Cushing

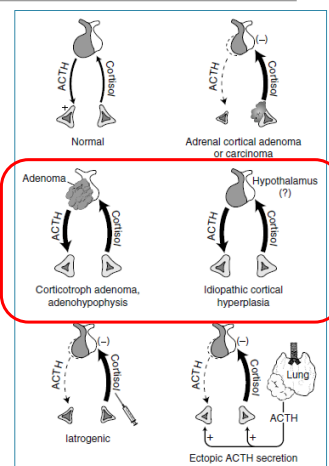
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Hipercortisolismo Pituitário-Dependente

Upregulation da secreção de ACTH secundário à tumor ou hiperplasia de corticotrofos hipofisários

Critérios ALIVE para Diagnóstico de HPD (1+2+3):

1. Identificação das características clínico-laboratoriais da SC
2. Demonstração excesso cortisol através de teste dinâmico
 - TSpBDD sangue, TSpADD sangue/urina, ou TEpA
3. Demonstração da ACTH-dependência por pelo menos um teste de diferenciação:
 - Supressão >50% em TSpBDD (sangue) ou TSpADD (sangue/urina)
 - Ausência de supressão ACTH
 - Ausência de imagem sugestiva de tumor adrenal
 - Alterações características em imagens (TC/RM) de hipófise



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Hipercortisolismo Adrenal-Dependente

Upregulation da secreção de cortisol 2ª a tumor ou hiperplasia de células do córtex adrenal

Critérios ALIVE para Diagnóstico de HAD (1+2+3):

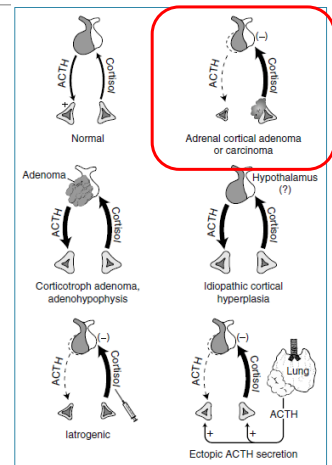
1. Identificação das características clínico-laboratoriais da SC

2. Demonstração excesso cortisol através de teste dinâmico

➤ TSpBDD sangue, TSpADD sangue/urina, ou TEPa

3. Demonstração da ACTH-independência por pelo menos um teste de diferenciação:

- ACTH suprimido
- Presença de tumor adrenal documentado por US, TC ou RM
- Evidências de atrofia adrenal contralateral



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Síndrome de Cushing latrogênica

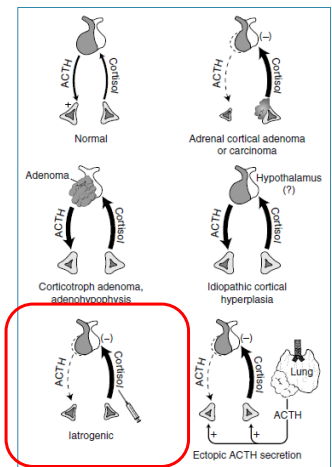
Forma de SC causada pela administração crônica de glicocorticoides tópicos ou sistêmicos

Critérios ALIVE para Diagnóstico SC latrogênica (1+2+3):

1. Histórico de ter recebido. ou estar recebendo, GC terapia crônica
2. Ausência de secreção de cortisol demonstrado por TEPACTH
3. Melhora dos sinais clínicos após interrupção GC terapia

Comentários:

- ✓ Síndrome semelhante pode ser causada por administração de progestágenos
- ✓ Interrupção súbita da terapia deve ser evitada devido ao risco de hipoadrenocorticism



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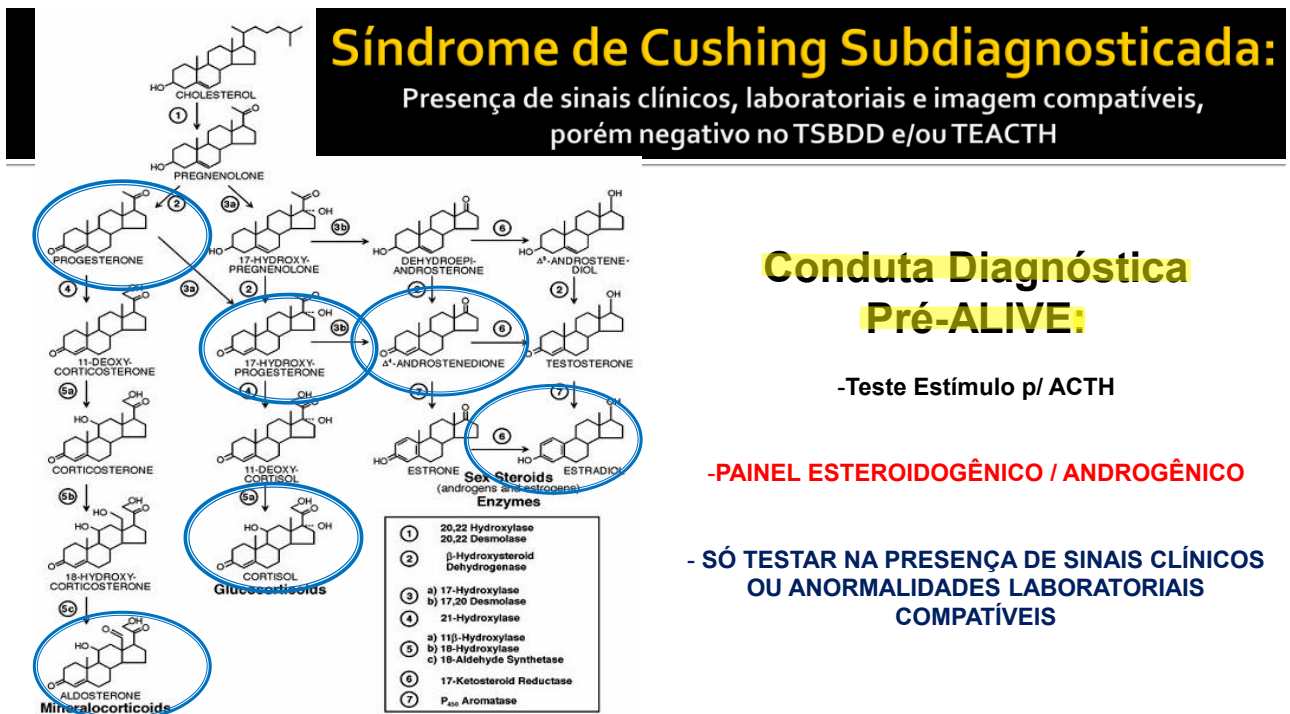
~~"HAC Atípico/Oculto"~~

Proposta ALIVE:

"Síndrome de Cushing Subdiagnosticada"

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Síndrome de Cushing subdiagnosticada (SCSD)

SCSD ACTH-DEPENDENTE

Síndrome de Cushing 2ª excesso ACTH com excesso de cortisol não documentável

Critérios:

- Sinais clínicos de SC
- Outras causas eliminadas
- Resultados normais testes dinâmicos
- ACTHe não suprimido
- Ausência de tumor adrenal
- ✓ Resultado de inacurácia dos valores de referência dos testes
 - ✓ Re-testar se persistência dos sinais?
 - ✓ Ensaio terapêutico?

SCSD ACTH-INDEPENDENTE

Síndrome de Cushing 2ª secreção de hormônios esteroides sem atividade GC (p.ex. P4, 17-OH-P) p/ TA

Critérios:

- Sinais clínicos de SC
- + resultados normais testes dinâmicos
- + um dos seguintes:
 - Presença de TA
 - ACTHe suprimido
- Critérios atendidos?
 - Caso +, desnecessária a identificação do "hormônio" para o tratamento ➔ ADRENALECTOMIA

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Journal of Veterinary Internal Medicine

Open Access



J Vet Intern Med 2015;29:193–199

Serum Cortisol Concentrations in Dogs with Pituitary-Dependent Hyperadrenocorticism and Atypical Hyperadrenocorticism

L.A. Frank, G.A. Henry, J.C. Whittemore, B.D. Enders, D.I. Mawby, and B.W. Rohrbach

Background: Atypical hyperadrenocorticism (AHAC) is considered when dogs have clinical signs of hypercortisolemia with normal hyperadrenocorticism screening tests.

Hypothesis/Objectives: To compare cortisol concentrations and adrenal gland size among dogs with pituitary-dependent hyperadrenocorticism (PDH), atypical hyperadrenocorticism (AHAC), and healthy controls.

Animals: Ten healthy dogs, 7 dogs with PDH, and 8 dogs with AHAC.

Methods: Dogs were prospectively enrolled between November 2011 and January 2013. Dogs were diagnosed with PDH or AHAC based on clinical signs and positive screening test results (PDH) or abnormal extended adrenal hormone panel results (AHAC). Transverse adrenal gland measurements were obtained by abdominal ultrasound. Hourly mean cortisol (9 samplings), sum of hourly cortisol measurements and adrenal gland sizes were compared among the 3 groups.

Results: Hourly (control, 1.4 ± 0.6 µg/dL; AHAC, 2.9 ± 1.3 ; PDH, 4.3 ± 1.5) (mean, SD) and sum (control, 11.3 ± 3.3 ; AHAC, 23.2 ± 7.7 ; PDH, 34.7 ± 9.9) cortisol concentrations differed significantly between the controls and AHAC ($P < .01$) and PDH ($P < .01$) groups. Hourly ($P < .01$) but not sum ($P = .27$) cortisol concentrations differed between AHAC and PDH dogs. Average transverse adrenal gland diameter of control dogs (5.3 ± 1.2 mm) was significantly less than dogs with PDH (6.4 ± 1.4 ; $P = .02$) and AHAC (7.2 ± 1.5 ; $P < .01$); adrenal gland diameter did not differ ($P = .18$) between dogs with AHAC and PDH.

Conclusions and Clinical Importance: Serum cortisol concentrations in dogs with AHAC were increased compared to controls but less than dogs with PDH, while adrenal gland diameter was similar between dogs with AHAC and PDH. These findings suggest cortisol excess could contribute to the pathophysiology of AHAC.

Key words: Adrenal; Atypical Cushing's Syndrome; Endocrine.

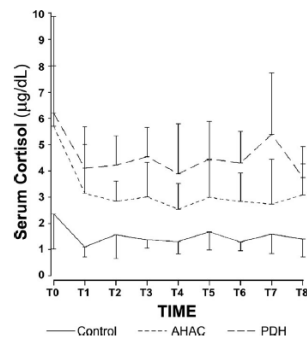


Fig 1. Hourly cortisol concentrations (mean, SD) of control dogs ($n = 10$), dogs with AHAC ($n = 8$), and dogs with PDH ($n = 7$). T0 mean cortisol for dogs with AHAC was significantly greater ($P < .01$) than other sampling times.

Table 1. Adrenal hormone concentrations before and after ACTH stimulation in 8 dogs with atypical hyperadrenocorticism (AHAC)

	Reference Interval*		Median (range)	
	Baseline	After Stimulation	Baseline	After Stimulation
Cortisol (µg/dL)	0.2–5.9	$\leq 22.0^†$	2.3 (1.6–9.0)	15.8 (12.7–17.7)
Androstenedione (ng/mL)	0.05–0.57	0.27–3.97	0.42 (0.21–3.94)	5.89 (1.32–8.42)
Estradiol (pg/mL)	30.8–69.9	27.9–69.2	78 (58.7–165.1)	73.8 (55.8–168.3)
Progesterone (ng/mL)	0.03–0.49	0.10–1.50	0.13 (<0.03–1.11)	1.78 (1.22–3.83)
17-OH Progesterone (ng/mL)	0.08–0.77	0.40–1.62	0.15 (<0.08–0.72)	1.78 (1.25–5.89)

*Reference intervals from University of Tennessee Veterinary Medical Center Clinical Endocrinology Service.

[†]Cortisol concentrations greater than 22.0 µg/dL considered diagnostic for HAC.

Table 2. Average transverse diameter (mm ± SD) of adrenal glands in control dogs ($n = 10$), dogs with AHAC ($n = 8$), and dogs with PDH ($n = 7$). Different letters indicate significant difference ($P < .01$).

	Left Adrenal	Right Adrenal	Average of Both Glands
Control	5.6 ± 1.1	5.0 ± 1.3	5.3 ± 1.2^a
AHAC	7.1 ± 1.5	7.2 ± 1.7	7.2 ± 1.5^b
PDH	6.3 ± 1.3	6.5 ± 1.6	6.4 ± 1.4^b

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STANDARD ARTICLE

Journal of Veterinary Internal Medicine **ACVIM**
Open Access American College of Veterinary Internal Medicine

Development and internal validation of a prediction tool to aid the diagnosis of Cushing's syndrome in dogs attending primary-care practice

Imogen Schofield¹ | David C. Brodbelt¹ | Stijn J. M. Niessen^{2,3} |
David B. Church² | Rebecca F. Geddes² | Noel Kennedy¹ | Dan G. O'Neill¹



Abstract

Background: Novel methods to aid identification of dogs with spontaneous Cushing's syndrome are warranted to optimize case selection for diagnostics, avoid unnecessary testing, and ultimately aid decision-making for veterinarians.

Hypothesis/Objectives: To develop and internally validate a prediction tool for dogs receiving a diagnosis of Cushing's syndrome using primary-care electronic health records.

Animals: Three hundred and ninety-eight dogs diagnosed with Cushing's syndrome and 541 noncase dogs, tested for but not diagnosed with Cushing's syndrome, from a cohort of 905 544 dogs attending VetCompass participating practices.

Methods: A cross-sectional study design was performed. A prediction model was developed using multivariable binary logistic regression taking the demography, presenting clinical signs and some routine laboratory results into consideration. Predictive performance of each model was assessed and internally validated through bootstrap resampling. A novel clinical prediction tool was developed from the final model.

Results: The final model included predictor variables sex, age, breed, polydipsia, vomiting, potbelly/hepatomegaly, alopecia, pruritus, alkaline phosphatase, and urine specific gravity. The model demonstrated good discrimination (area under the receiver operating curve [AUROC] = 0.78 [95% CI = 0.75–0.81]; optimism-adjusted AUROC = 0.76) and calibration (C-slope = 0.86). A tool was developed from the model which calculates the predicted likelihood of a dog having Cushing's syndrome from 0% (score = −13) to 96% (score = 10).

Conclusions and Clinical Importance: A tool to predict a diagnosis of Cushing's syndrome at the point of first suspicion in dogs was developed, with good predictive

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	Category	Points	Points scored
Dog demography			
Neuter status	Female-entire	0	
	Female-neutered	−1	
	Male-entire	−1	
	Male-neutered	−1	
Current age (years)	<7	0	
	≥7	1	
Breed	Bichon frise	2	
	Border terrier	1	
	Labrador retriever	−3	
	Schnauzer	−2	
	West Highland white terrier	−3	
	Other breed or crossbreed	0	
Presenting clinical signs			
Polydipsia	Yes	2	
	No	0	
Vomiting	Yes	−2	
	No	0	
Potbelly/hepatomegaly	Yes	3	
	No	0	
Alopecia	Yes	2	
	No	0	
Pruritus	Yes	−2	
	No	0	
Laboratory factors			
Urine specific gravity	Dilute (≤ 1.020)	0	
	Not dilute (> 1.020)	−2	
	Not recorded	−1	
Serum ALKP	Elevated	0	
	Not elevated	−3	
	Not recorded	0	
		Total score:	

TABLE 6 Points total and predicted likelihood of an individual dog having Cushing's syndrome using demographic, clinical sign, and laboratory predictive factors, developed in dogs attending primary-care veterinary practices in the United Kingdom (cases, n = 398; noncases: n = 541)

Points total	Predicted likelihood of Cushing's syndrome (0.00 = 0%; 0.96 = 96%)
−13	0.00
−12	0.01
−11	0.01
−10	0.01
−9	0.02
−8	0.03
−7	0.04
−6	0.05
−5	0.08
−4	0.11
−3	0.15
−2	0.20
−1	0.27
0	0.35
1	0.44
2	0.53
3	0.63
4	0.71
5	0.78
6	0.84
7	0.88
8	0.92
9	0.94
10	0.96

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Obrigado pela
Atenção!



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SÍNDROME DE CUSHING

Parte II

Prof. Dr. Álan Gomes Pöppl

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Objetivos do Tratamento da Síndrome de Cushing (ALIVE-ESVE)

- Otimizar QdV,
 - Eliminar sinais clínicos,
 - Reduzir complicações e mortalidade
-
- Objetivos são alcançados **eliminando a fonte de secreção excessiva de ACTH, e/ou de hormônios adrenais; ou ao menos, controlando a secreção hormonal das adrenais sem induzir hipoadrenocorticismismo**



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Objetivos do Tratamento da Síndrome de Cushing (ALIVE-ESVE)

- *Ideal world*: só tratar pacientes com sinais clínicos consistentes com síndrome de Cushing e após confirmação da doença por meio de testes endócrinos.
- Diferenciação das formas de ocorrência natural (HPD x HAD) é altamente desejável para otimizar estratégias terapêuticas
- SC Iatrogênica é tratada com redução gradual da administração de GC

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Quais as Opções de Tratamento Disponíveis?

HIPÓFISE (Pituitary-target) → Eficácia somente no HPD (ACTH-dependente)

Terapia	Disponibilidade	Custo	Eficácia	Risco
Hipofisectomia (padrão-ouro)	√ (RJ, RS, SP)	\$\$\$\$	↑↑↑↑↑	↑↑↑↑↑
Radioterapia (macroadenomas)	√ (SP, RJ)	\$\$\$\$\$	↑ - ↑↑↑	↑↑↑
Pasireotide (Análogo STT)	√ (importado)	\$\$\$\$\$	Ø - ↑↑↑	↓
Ácido Retinóico (Isotretinoína)	√√	\$\$\$	Ø - ↑↑	↑↑
Selegilina (Inibidora MAO)	√√√	\$\$	Ø - ↑	↓
Cabergolina (Agonista D ₂)	√√√	\$\$	Ø - ↑↑↑	↑

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Quais as Opções de Tratamento Disponíveis?

ADRENAL (Adrenal-target) → Eficácia em ACTH-dependente e ACTH-independente

Terapia	Disponibilidade	Custo	Eficácia	Risco
Adrenalectomia (padrão-ouro)	√√	\$\$\$\$	↑↑↑↑↑	↑↑↑
Radioterapia (invasão/carcinomas)	√ (SP, RJ)	\$\$\$\$\$	Ø - ↑↑	↑↑↑
Mitotano (adrenocorticolítico)	√√	\$\$\$\$	↑↑↑↑	↑↑↑
Cetoconazol (Antifúngico)	√√√	\$ - \$\$	Ø - ↑↑	↑↑
Melatonina (Indolamina)	√√√	\$ - \$\$	Ø - ↑↑	↓
Trilostano (Esteróide sintético)	√√√	\$ - \$\$\$	↑↑↑↑	↑

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A Origem da Trilostanomania

Há não muito tempo atrás, em consultórios não muito distantes...

Uma nova droga sintética foi testada e aprovada (2005) para uso em cães com HAC no Reino Unido. Em pouco tempo, tornou-se a principal modalidade de tratamento médico da doença ao redor do mundo, em substituição ao malvado e perigoso Mitotano...

Apesar disso, alguns aspectos sobre o trilostano ainda precisam ser melhor estudados.

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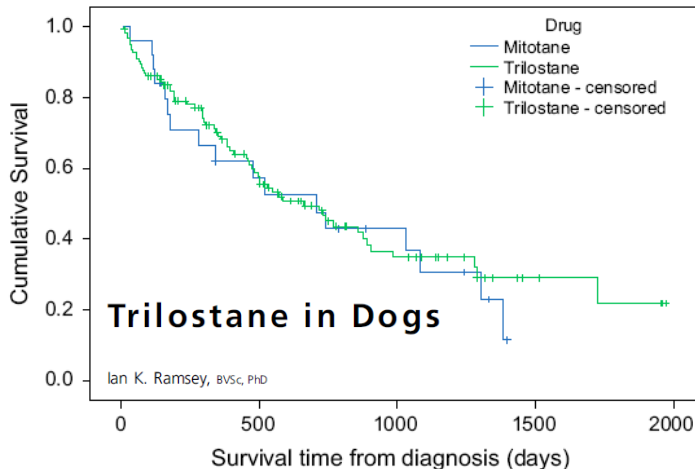
MITOTANOFOBIA...

HIPOADRENOCORTICISMO
"Síndrome de Addison"



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TRILOSTANO vs. MITOTANO



Trilostano eficácia entre 68 e 100%
Mitotano eficácia em torno de 80%

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Arq. Bras. Med. Vet. Zootec.

A retrospective cohort study of 122 dogs treated for hypercortisolism: low-dose dexamethasone suppression test sensitivity and comparative outcomes in response to mitotane or trilostane

[Estudo de coorte retrospectivo de 122 cães que receberam tratamento para hipercolesterolemia: sensibilidade do teste de supressão por baixa dose de dexametasona e comparação entre os desfechos em relação ao mitotano ou ao trilostano]

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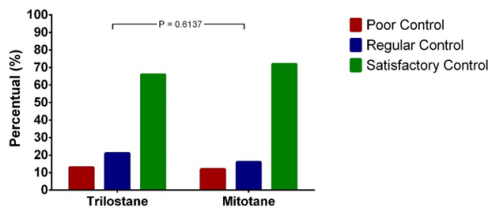


Figure 4. Distribution of hypercortisolism degree of control in the opinion of the dog owners according to the treatment adopted (mitotane or trilostane) over time.

Table 1. Medical treatment was applied to a population of 122 dogs with hypercortisolism according to disease classification and reported outcomes

	Trilostane (n=71)	Mitotane (n=51)	Shifted	IHA
Disease Classification				
PDH (n = 101)	63 (62.4%)	38 (37.6%)	6 (5.9%)	6 (5.9%)
ADH (n = 12)	4 (33.3%)	8 (66.6%)	1 (8.3%)	1 (8.3%)
SDCS (n = 6)	3 (50%)	3 (50%)	-	-
PDH + AN (n=3)	1 (33.3%)	2 (66.6%)	-	-
Disease Control				
Good	47 (66.2%)	37 (72.5%)	-	7 (8.3%)
Moderate	15 (21.1%)	8 (15.7%)	-	-
Poor	9 (12.6%)	6 (11.7%)	7 (46.7%)	-
IHA	5 (7.04%)	2 (3.92%)	-	-
Survival (months)	31 (4 - 95)	36 (9 - 90)	NA	NA

PDH: pituitary-dependent hypercortisolism, ADH: adrenal-dependent hypercortisolism, SDSC: sub-diagnostic Cushing's syndrome, AN: adrenal neoplasia, IHA: iatrogenic hypoadrenocorticism, NA: not applicable.

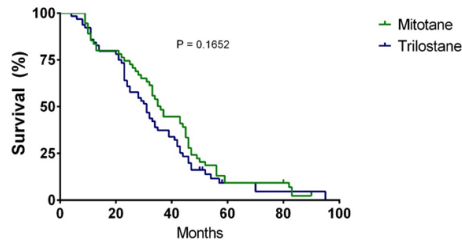
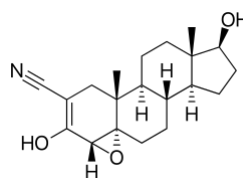


Figure 5. Kaplan-Meier plots of patients' survival according to the hypercortisolism treatment chosen (Mitotane x Trilostane) in a population of 122 dogs.

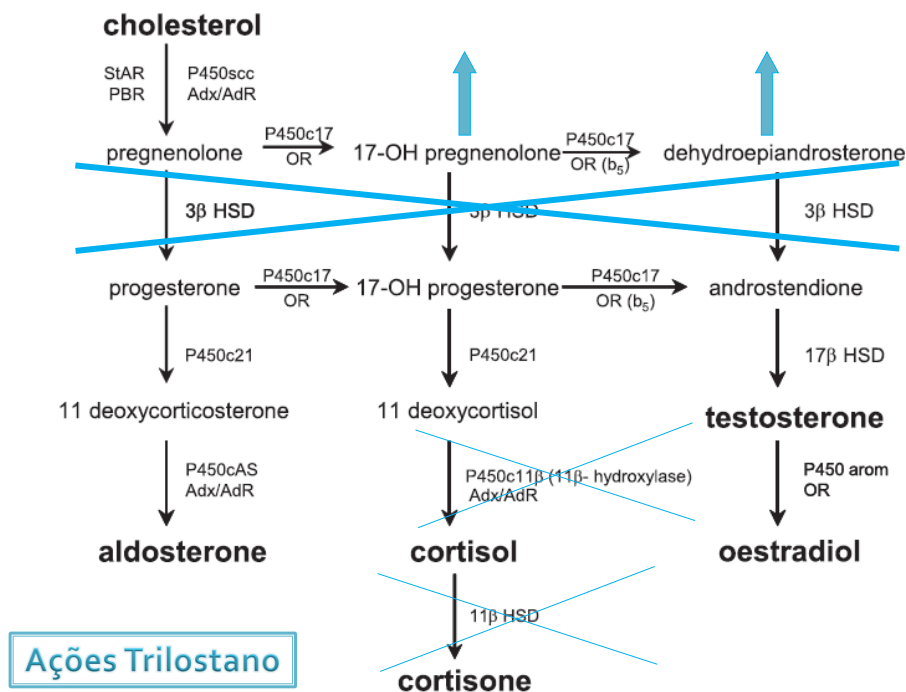
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TRILOSTANO

- ✓ Esteróide sintético que atua como inibidor competitivo da síntese de esteróides (INIBIÇÃO DA 3β -HSD)
- ✓ Metabolização hepática → diversos metabólitos, incluindo cetotrilostano que também é ativo
- ✓ Pico de absorção ~ 90 min
- ✓ Duração efeito → máximo de 12-18 h
- ✓ Administração SEMPRE junto Alimento!
 - ✓ Absorção nula em jejum



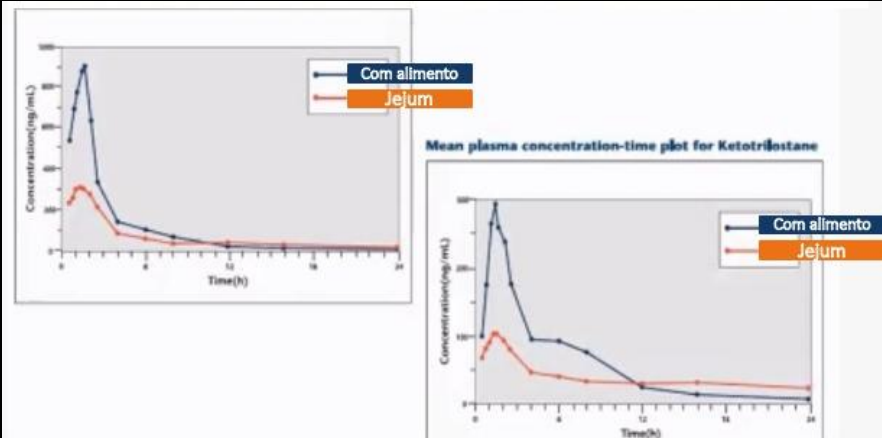
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Administração Sempre com Alimento

- *Concentrações plasmáticas de trilostano e do metabólito cetotrilostano após administração com alimento ou em jejum*



GRAHAM, Workshop Pesquisa Hormonais, 2020

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TRILOSTANO – Manipulação

ORIGINAL STUDIES

(J Am Anim Hosp Assoc 2012; 48:228–233. DOI 10.5326/JAAHA-MS-5763)

Pharmaceutical Evaluation of Compounded Trilostane Products

Audrey K. Cook, BVMS, Coriella D. Nieuwoudt, PharmD, Susan L. Longhofer, MS, DVM

This study was supported by an unrestricted gift from Dechra Ltd., Overland Park, KS. The authors would like to thank Davida Scanlin and Phil Driver for their technical assistance.

TABLE 1

Number and Percentage of Compounded Capsules and Controls that Met Each of the Acceptance Criteria

	Trilostane content	Impurity/related substance	Dissolution
Acceptance criteria	90–105%	≤2%	≥70% by 75 min
Compounded capsules	60/96 (63%)	95/96 (99%)	77/96 (80%)
Compounded controls (CC)	8/8 (100%)	8/8 (100%)	8/8 (100%)
Proprietary capsules (PC)	8/8 (100%)	8/8 (100%)	8/8 (100%)

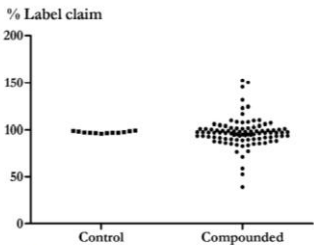


FIGURE 1 Average percent label claim (% LC) for control (n=12) and compounded (n=96) batches of trilostane.

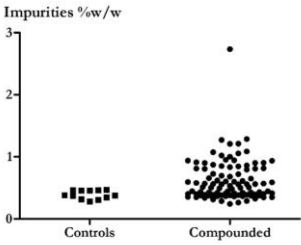


FIGURE 2 Average percent (% weight/weight [w/w]) impurities/related substances for control (n=12) and compounded (n=96) batches of trilostane.

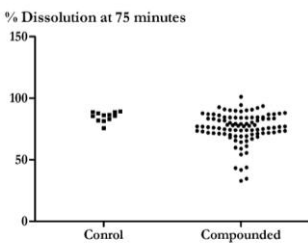


FIGURE 3 Average dissolution based on % LC for control (n=12) and compounded (n=96) batches of trilostane at 75 min.

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TRILOSTANO – Dose tem sido debatida internacionalmente

- Dose Bula Inicial x Dose Atual:
- Atualmente 0,5- 1 mg/kg bid
- (1 mg/kg bid ou 2 mg/kg sid)

Pes

Evaluation of twice-daily lower-dose trilostane treatment administered orally in dogs with naturally occurring hyperadrenocorticism (dia)

Edward C. Feldman, DVM, DACVM

Objective—To evaluate effectiveness and incidence of adverse reactions to twice-daily lower-dose oral administration of trilostane in the treatment of dogs with naturally occurring hyperadrenocorticism (NOH).

Design—Clinical trial.

Animals—47 dogs with NOH.

Procedures—47 dogs were treated orally with trilostane (0.21 to 1.1 mg/kg [0.1 to 0.5 mg/kg], q 12 h). All dogs were reevaluated at 2 weeks and 2 months, 38 dogs at 6 months, and 28 dogs at 1 year of treatment.

Results—9 of 47 dogs had an adrenocortical tumor causing NOH, and all had good responses after 2 months (mean trilostane dosage, 0.89 mg/kg [0.40 mg/kg], q 12 h). All successfully underwent surgical adrenal tumor extirpation. Thirty-eight dogs had pituitary-dependent hyperadrenocorticism (PDH); 15 dogs did not require a dose increase during the study, and at each of 4 reevaluations, 10 of 15, 13 of 15, 14 of 15, and 11 of 11 had a good response. Twenty-three dogs with PDH had their dose or frequency of trilostane administration increased during the study. Mean trilostane dosage at 1-year reevaluation in dogs with a good response was 1.7 mg/kg (0.8 mg/kg), twice daily, or 1.1 mg/kg, 3 times daily. At each of 4 reevaluations, 17 of 22, 14 of 23, 17 of 23, and 13 of 17 dogs with PDH had a good response. Five dogs became ill because of trilostane-induced adverse effects, but only 1 required hospitalization.

Conclusions and Clinical Relevance—Administration of initial lower doses of trilostane to dogs with NOH is effective. *J Am Vet Med Assoc* 2011;238:1441–1451

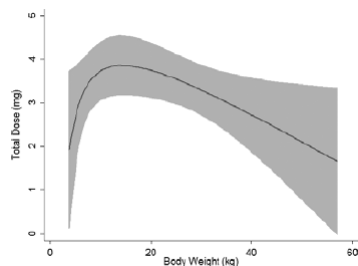
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TRILOSTANO – Impacto Porte

J Vet Intern Med 2012;26:1078–1080

Trilostane Dose versus Body Weight in the Treatment of Naturally Occurring Pituitary-Dependent Hyperadrenocorticism in Dogs

E.C. Feldman and P.H. Kass



TENDÊNCIA:

- Qto < cão > dose/kg
- Qto > cão < dose/kg

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Monitoramento Clínico Terapia com Trilostano

❖ Avaliações clínicas periódicas!

❖ Ajustes de dose baseados principalmente na clínica

❖ Exames gerais nas revisões de acordo com cada caso

❖ Na/K e Cortisol



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Monitoramento Escore Clínico SC

- Monitoramento sistematizado dos Sinais Clínicos!
- Nenhum parâmetro laboratorial é capaz de distinguir melhor pacientes bem controlados x mau controle
- Ideal escore menor possível

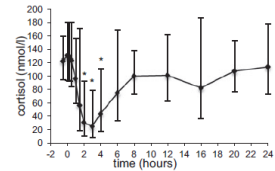


Article
Agreeing Language in Veterinary Endocrinology (ALIVE):
Cushing's syndrome and hypoadrenocorticism – a modified
Delphi-method-based system to create consensus definitions

Stijn JM. Nissem^{1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100,101,102,103,104,105,106,107,108,109,110,111,112,113,114,115,116,117,118,119,120,121,122,123,124,125,126,127,128,129,130,131,132,133,134,135,136,137,138,139,140,141,142,143,144,145,146,147,148,149,150,151,152,153,154,155,156,157,158,159,160,161,162,163,164,165,166,167,168,169,170,171,172,173,174,175,176,177,178,179,180,181,182,183,184,185,186,187,188,189,190,191,192,193,194,195,196,197,198,199,200,201,202,203,204,205,206,207,208,209,210,211,212,213,214,215,216,217,218,219,220,221,222,223,224,225,226,227,228,229,230,231,232,233,234,235,236,237,238,239,240,241,242,243,244,245,246,247,248,249,250,251,252,253,254,255,256,257,258,259,260,261,262,263,264,265,266,267,268,269,270,271,272,273,274,275,276,277,278,279,280,281,282,283,284,285,286,287,288,289,290,291,292,293,294,295,296,297,298,299,300,301,302,303,304,305,306,307,308,309,310,311,312,313,314,315,316,317,318,319,320,321,322,323,324,325,326,327,328,329,330,331,332,333,334,335,336,337,338,339,340,341,342,343,344,345,346,347,348,349,350,351,352,353,354,355,356,357,358,359,360,361,362,363,364,365,366,367,368,369,370,371,372,373,374,375,376,377,378,379,380,381,382,383,384,385,386,387,388,389,390,391,392,393,394,395,396,397,398,399,400,401,402,403,404,405,406,407,408,409,410,411,412,413,414,415,416,417,418,419,420,421,422,423,424,425,426,427,428,429,430,431,432,433,434,435,436,437,438,439,440,441,442,443,444,445,446,447,448,449,450,451,452,453,454,455,456,457,458,459,460,461,462,463,464,465,466,467,468,469,470,471,472,473,474,475,476,477,478,479,480,481,482,483,484,485,486,487,488,489,490,491,492,493,494,495,496,497,498,499,500,501,502,503,504,505,506,507,508,509,510,511,512,513,514,515,516,517,518,519,520,521,522,523,524,525,526,527,528,529,530,531,532,533,534,535,536,537,538,539,540,541,542,543,544,545,546,547,548,549,550,551,552,553,554,555,556,557,558,559,560,561,562,563,564,565,566,567,568,569,570,571,572,573,574,575,576,577,578,579,580,581,582,583,584,585,586,587,588,589,590,591,592,593,594,595,596,597,598,599,600,601,602,603,604,605,606,607,608,609,610,611,612,613,614,615,616,617,618,619,620,621,622,623,624,625,626,627,628,629,630,631,632,633,634,635,636,637,638,639,640,641,642,643,644,645,646,647,648,649,650,651,652,653,654,655,656,657,658,659,660,661,662,663,664,665,666,667,668,669,670,671,672,673,674,675,676,677,678,679,680,681,682,683,684,685,686,687,688,689,690,691,692,693,694,695,696,697,698,699,700,701,702,703,704,705,706,707,708,709,710,711,712,713,714,715,716,717,718,719,720,721,722,723,724,725,726,727,728,729,730,731,732,733,734,735,736,737,738,739,740,741,742,743,744,745,746,747,748,749,750,751,752,753,754,755,756,757,758,759,760,761,762,763,764,765,766,767,768,769,770,771,772,773,774,775,776,777,778,779,780,781,782,783,784,785,786,787,788,789,790,791,792,793,794,795,796,797,798,799,800,801,802,803,804,805,806,807,808,809,810,811,812,813,814,815,816,817,818,819,820,821,822,823,824,825,826,827,828,829,830,831,832,833,834,835,836,837,838,839,840,841,842,843,844,845,846,847,848,849,850,851,852,853,854,855,856,857,858,859,860,861,862,863,864,865,866,867,868,869,870,871,872,873,874,875,876,877,878,879,880,881,882,883,884,885,886,887,888,889,890,891,892,893,894,895,896,897,898,899,900,901,902,903,904,905,906,907,908,909,910,911,912,913,914,915,916,917,918,919,920,921,922,923,924,925,926,927,928,929,930,931,932,933,934,935,936,937,938,939,940,941,942,943,944,945,946,947,948,949,950,951,952,953,954,955,956,957,958,959,960,961,962,963,964,965,966,967,968,969,970,971,972,973,974,975,976,977,978,979,980,981,982,983,984,985,986,987,988,989,990,991,992,993,994,995,996,997,998,999,1000,1001,1002,1003,1004,1005,1006,1007,1008,1009,1010,1011,1012,1013,1014,1015,1016,1017,1018,1019,1020,1021,1022,1023,1024,1025,1026,1027,1028,1029,1030,1031,1032,1033,1034,1035,1036,1037,1038,1039,1040,1041,1042,1043,1044,1045,1046,1047,1048,1049,1050,1051,1052,1053,1054,1055,1056,1057,1058,1059,1060,1061,1062,1063,1064,1065,1066,1067,1068,1069,1070,1071,1072,1073,1074,1075,1076,1077,1078,1079,1080,1081,1082,1083,1084,1085,1086,1087,1088,1089,1090,1091,1092,1093,1094,1095,1096,1097,1098,1099,1100,1101,1102,1103,1104,1105,1106,1107,1108,1109,1110,1111,1112,1113,1114,1115,1116,1117,1118,1119,1120,1121,1122,1123,1124,1125,1126,1127,1128,1129,1130,1131,1132,1133,1134,1135,1136,1137,1138,1139,1140,1141,1142,1143,1144,1145,1146,1147,1148,1149,1150,1151,1152,1153,1154,1155,1156,1157,1158,1159,1160,1161,1162,1163,1164,1165,1166,1167,1168,1169,1170,1171,1172,1173,1174,1175,1176,1177,1178,1179,1180,1181,1182,1183,1184,1185,1186,1187,1188,1189,1190,1191,1192,1193,1194,1195,1196,1197,1198,1199,1200,1201,1202,1203,1204,1205,1206,1207,1208,1209,1210,1211,1212,1213,1214,1215,1216,1217,1218,1219,1220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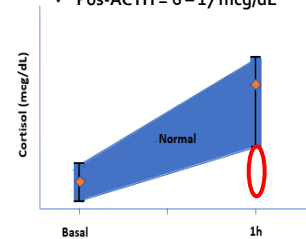
Monitoramento Hormonal

- Diferentes estratégias, nenhuma 100% validada...
- Teste Estimulação por ACTH 2-3 h após dar trilostano
 - ✓ Faixa alvo: cortisol pós-ACTH entre 1,5-5 mcg/dL
 - ✓ Indicado pacientes muito bem clinicamente para avaliar segurança em manter a dose, ou avaliar necessidade redução de dose
- Cortisol pré-trilostano (12h pós-trilostano)
 - ✓ Faixa alvo: cortisol basal entre 1,5-5 mcg/dL
 - ✓ Útil para avaliar segurança em aumento da dose em paciente clinicamente mau-controlado
- Cortisol 3h pós-trilostano
 - ✓ Faixa alvo: cortisol basal entre 1-2,5 mcg/dL
 - ✓ Útil para avaliar segurança em aumento da dose em paciente clinicamente mau-controlado



Valores de Referência Cortisol:

- ✓ Basal = 0,5 – 6 mcg/dL
- ✓ Pós-ACTH = 6 – 17 mcg/dL



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Monitoramento Hormonal: Teste de Estimulação por ACTH

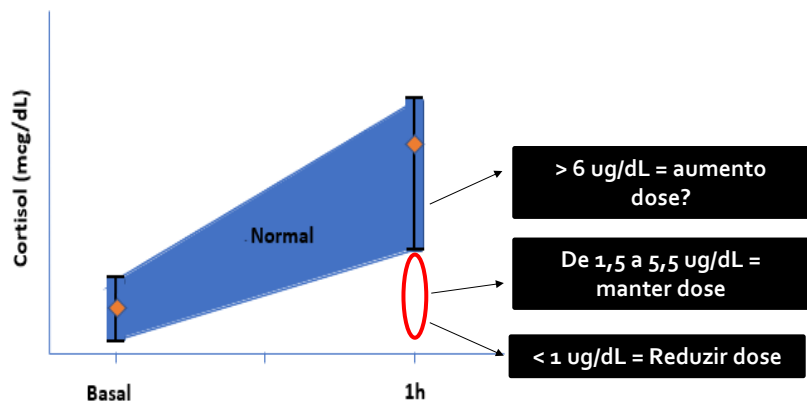
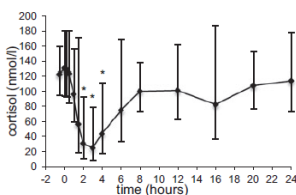
- Aumentos de dose baseados nos sinais clínicos:
- Estimulação com ACTH (1- 5mcg/kg, IV)

Testar 2 a 4 horas
após dar trilostano

J Vet Intern Med 2014;28:380-385

Effect of Trilostane on Hormone and Serum Electrolyte Concentrations in Dogs with Pituitary-Dependent Hyperadrenocorticism

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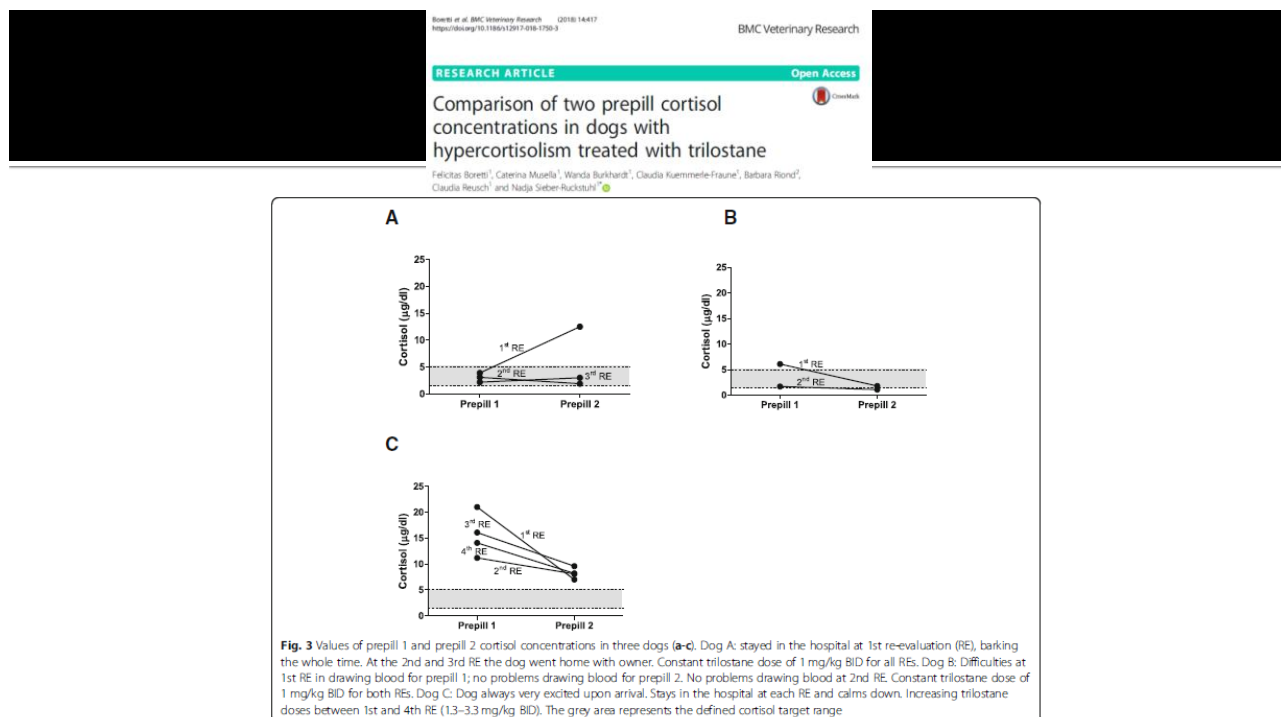
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Monitoramento Hormonal: Cortisol Basal Pré-Trilostano ou 3h Pós-Trilostano

- Cortisol pré-pílula, ou 3h pós-trilostano (*Pre-pill melhor desempenho*)
- Cortisol pré-pílula 1,5 a 5 mcg/dL* e/ou = bom controle,
- Cortisol 3h pós-trilostano 1 e 2,5 mcg/dL* = bom controle,
- * Immulite 2000 cortisol; Siemens
- Sempre associado a avaliação clínica
- CONTRA-INDICADO: comorbidades, animais estressados
- Autores argumentam que foi mais fiel que cortisol pós-ACTH em relação a opinião tutor sobre grau de controle



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84

Abstract

Background: Results of ACTH stimulation test (ACTHst), pre- and post-trilostane serum cortisol concentrations (SCCs), urine concentration (urine-specific gravity [USG]), and urine cortisol : creatinine ratios (UCCRs) are common variables used to monitor trilostane treatment of dogs with pituitary-dependent hyperadrenocorticism (PDH). However, none has consistently discriminated dogs receiving an adequate dose (A) from those overdosed (O) or underdosed (U).

Objectives: To assess and compare recommended monitoring variables, including serial SCCs in a cohort of dogs with PDH treated with trilostane.

Animals: Privately owned dogs with PDH (n = 22) and 3 healthy dogs (controls).

Methods: Prospective, multicenter, 2-day study. On day "a" (randomized): ACTHst was completed. Day "b" (>2 to <7 days later): SCCs were assessed ~0.5 hours, immediately before, and 1, 2, 2.5, 3, 3.5, 4, 6, 8, and 12 hours after trilostane administration. On the first study day, urine collected at home was assessed for USG, UCCR and owner opinions regarding PDH were categorized as: A (clinical signs resolved), U (remains symptomatic), or ill (possible O).

Results: At 27 pairs of evaluations, 7 dogs were categorized as A, 19 U, and 1 possible O (excluded from the study). There was overlap in SCC results from the A and U dogs at every time point. Results of USG, UCCR, and ACTHst did not discriminate A from U dogs. Trilostane suppresses SCC within 1 hour of administration and its duration of action in most PDH dogs is <8 hours.

Conclusions and Clinical Importance: No single variable or group of variables reliably discriminated A dogs from U dogs during trilostane treatment for PDH.

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STANDARD ARTICLE

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Laboratory assessment of trilostane treatment in dogs with pituitary-dependent hyperadrenocorticism

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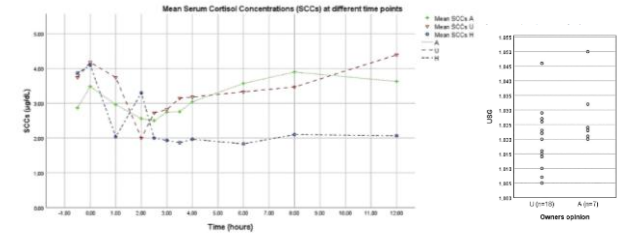


FIGURE 6 This graphs represents the cortisol curve performed on "day b." SCC throughout the day for dogs in the adequately dose (A), underdosed (U) group, and healthy (H). The healthy dogs did not receive trilostane. SCC, serum cortisol concentration

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STANDARD ARTICLE

Journal of Veterinary Internal Medicine **ACVIM**
American College of Veterinary Internal Medicine

Development and evaluation of a health-related quality-of-life tool for dogs with Cushing's syndrome

Imogen Schofield¹ | Dan G. O'Neill¹ | Dave C. Brodbelt¹ | David B. Church² | Rebecca F. Geddes² | Stijn J. M. Niessen^{2,3}

TABLE 1 Final items included in the Cushing's syndrome HRQoL tool (CushQoL-pet) after question refinement

- 1 My dog is excessively thirsty
All the time (3), often (2), occasionally (1), never (0)
- 2 My dog urinates in the house
All the time (3), often (2), occasionally (1), never (0)
- 3 My dog is excessively hungry
All the time (3), often (2), occasionally (1), never (0)
- 4 My dog pants excessively
All the time (3), often (2), occasionally (1), never (0)
- 5 My dog appears to be gaining weight
All the time (3), often (2), occasionally (1), never (0)
- 6 My dog is depressed and quiet
All the time (3), often (2), occasionally (1), never (0)
- 7 My dog has no energy
All the time (3), often (2), occasionally (1), never (0)
- 8 My dog doesn't want to interact with other people / dogs
All the time (3), often (2), occasionally (1), never (0)
- 9 My dog is reluctant to play with me
All the time (3), often (2), occasionally (1), never (0)
- 10 My dog seems disorientated/confused
All the time (3), often (2), occasionally (1), never (0)

- 10 My dog seems disorientated/confused
All the time (3), often (2), occasionally (1), never (0)
- 11 My dog's hair coat is in a poor condition
All the time (3), often (2), occasionally (1), never (0)
- 12 My dog's skin appears to be uncomfortable (eg, dry/tight)
All the time (3), often (2), occasionally (1), never (0)
- 13 My dog appears to be in poor physical condition (eg, muscle loss/big belly)
All the time (3), often (2), occasionally (1), never (0)
- 14 I feel my dog's appearance gets negative comments
All the time (3), often (2), occasionally (1), never (0)
- 15 My dog struggles to walk very far
All the time (3), often (2), occasionally (1), never (0)
- 16 I worry about the future health of my dog
All the time (3), often (2), occasionally (1), never (0)
- 17 Mine and my dog's daily routine is being disrupted
All the time (3), often (2), occasionally (1), never (0)
- 18 I feel I am struggling to manage my dog's health
All the time (3), often (2), occasionally (1), never (0)
- 19 Currently I feel there is a strong bond between me and my dog
All the time (0), often (1), occasionally (2), never (3)

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0 - 57
Pontos

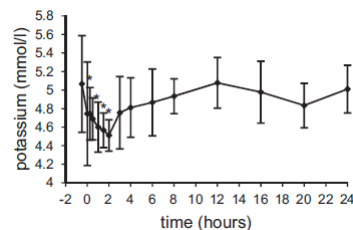
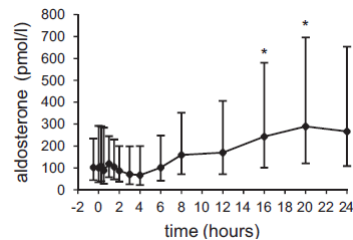
TRILOSTANO / complicações

- Bem tolerado na maioria dos casos (anorexia, êmese, diarreia)
- Hipercalemia
- Efeito potencialmente 2º a inibição da aldosterona

J Vet Intern Med 2014;28:160-165

Effect of Trilostane on Hormone and Serum Electrolyte Concentrations in Dogs with Pituitary-Dependent Hyperadrenocorticism

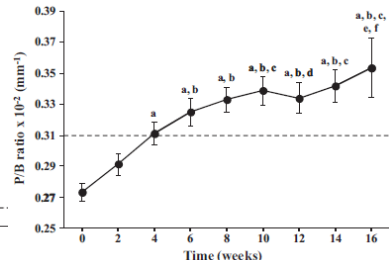
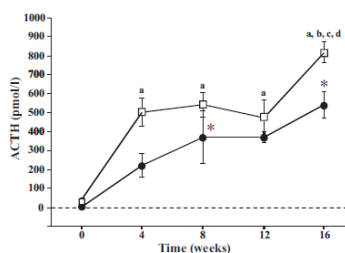
C. Griebisch, C. Lehnert, G.J. Williams, K. Failing, and R. Neiger



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O que Aprendemos com o Tempo sobre o Tratamento com Trilostano?

- A supressão da produção do cortisol anula o feedback negativo sobre eixo hipotálamo-hipófise-adrenal levando a:
- ↑ [ACTHe]
- Hiperplasia Corticotrofos



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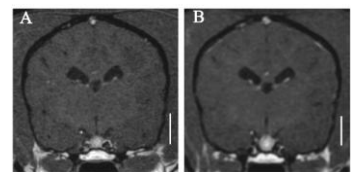
Domestic Animal Endocrinology 36 (2009) 52–64

DOMESTIC ANIMAL ENDOCRINOLOGY

www.journals.elsevierhealth.com/periodicals/dae

Trilostane-induced inhibition of cortisol secretion results in reduced negative feedback at the hypothalamic–pituitary axis

Takahiro Teshima^{a,*}, Yasushi Hara^a, Susumu Takekoshi^b, Yoshinori Nezu^a, Yasuji Harada^a, Takuya Yogo^a, Akira Teramoto^a, Robert Y. Osamura^c, Masahiro Tagawa^a



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O que Aprendemos com o Tempo sobre o Tratamento com Trilostano?

- A supressão da produção do cortisol anula o feedback negativo sobre eixo hipotálamo-hipófise-adrenal levando a:
 - ↑ [ACTHe]
 - Hiperplasia Corticotrofos
 - Hiperplasia Córtex Adrenal
 - ↑ Expressão ACTH-R Adrenais



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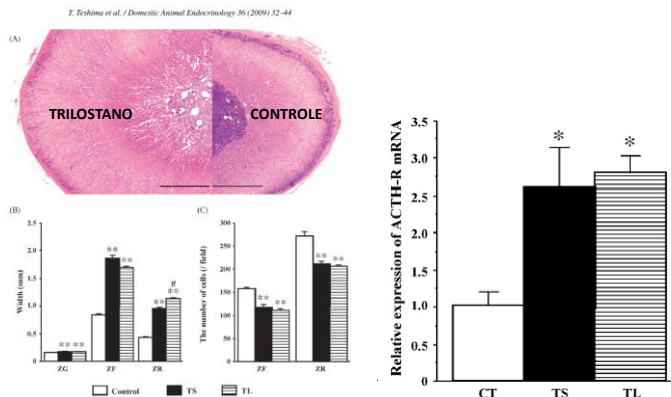
Domestic Animal Endocrinology 36 (2009) 32–44

DOMESTIC
ANIMAL
ENDOCRINOLOGY

www.elsevier.com/locate/domendo

Trilostane-induced inhibition of cortisol secretion results in reduced negative feedback at the hypothalamic–pituitary axis

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Robert Y. Osamura^b, Masahiro Tagawa^a



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O que Aprendemos com o Tempo sobre o Tratamento com Trilostano?

- A elevação crônica do ACTH endógeno em resposta ao trilostano predispõe a hemorragias e degeneração adrenal



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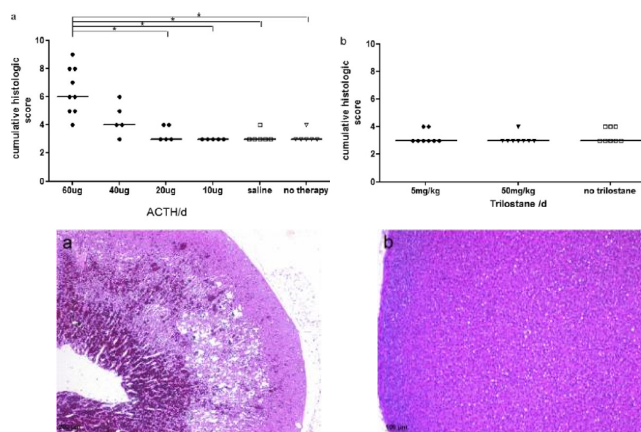
Domestic Animal Endocrinology 40 (2011) 155–164

DOMESTIC
ANIMAL
ENDOCRINOLOGY

www.elsevier.com/locate/domendo

Adrenocorticotrophic hormone, but not trilostane, causes severe adrenal hemorrhage, vacuolization, and apoptosis in rats

W.A. Burkhardt^a, F. Gussetti^b, F.S. Boretti^a, A. Ivoš Todesco^a, N. Aldajarov^b,
T.A. Lutz^a, C.E. Reusch^a, N.S. Sieber-Ruckstuhl^{a,b}



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O que Aprendemos com o Tempo sobre o Tratamento com Trilostano?

- Sua eficácia e segurança são melhores quando empregado em doses menores e com a dose dividida 2x ao dia (ou mais...)

Evaluation of twice-daily lower-dose trilostane treatment administered orally in dogs with naturally occurring hyperadrenocorticism

Edward C. Feldman, DVM, DACVP

Objective—To evaluate effectiveness and incidence of adverse reactions to twice-daily lower-dose oral administration of trilostane in the treatment of dogs with naturally occurring hyperadrenocorticism (NCH).

Design—Clinical trial.

Animals—47 dogs with NCH.

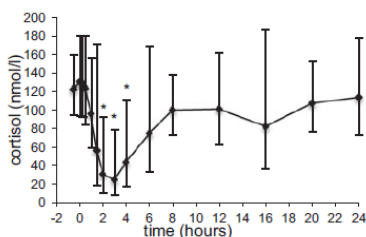
Procedures—47 dogs were treated orally with trilostane (0.21 to 1.1 mg/kg [0.1 to 0.5 mg/lb], q 12 h). All dogs were reevaluated at 2 weeks and 2 months, 38 dogs at 6 months, and 28 dogs at 1 year of treatment.

Results—8 of 47 dogs had an adrenocortical tumor causing NCH, and all had good responses after 2 months (mean trilostane dosage, 0.88 mg/kg [0.40 mg/lb], q 12 h). All successfully underwent surgical adrenal tumor resection. Thirty-eight dogs had pituitary-dependent hyperadrenocorticism (PDH); 15 dogs did not require a dose increase during the study, and at each of 4 reevaluations, 12 of 16, 12 of 16, 14 of 16, and 11 of 11 had a good response. Twenty-three dogs with PDH had their dose or frequency of trilostane administration increased during the study. Mean trilostane dosage at 1-year reevaluation in dogs with a good response was 1.7 mg/kg (0.8 mg/lb), twice daily, or 1.1 mg/kg, 3 times daily. At each of 4 reevaluations, 17 of 22, 14 of 22, 17 of 22, and 13 of 17 dogs with PDH had a good response. Five dogs became ill because of trilostane-induced adverse effects, but only 1 required hospitalization.

Conclusions and Clinical Relevance—Administration of initial lower doses of trilostane to dogs with NCH is effective. *J Am Vet Med Assoc* 2011;238:1441–1451.

J Vet Intern Med 2014;28:160–165

Effect of Trilostane on Hormone and Serum Electrolyte Concentrations in Dogs with Pituitary-Dependent



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O que Aprendemos com o Tempo sobre o Tratamento com Trilostano?

- Sua eficácia e segurança são melhores quando empregado em doses menores e com a dose dividida 2x ao dia (ou mais...)
- 15% casos em 24 meses,
- 26% em 48 meses
- HipoA transiente mais comum
- Quanto > tempo de tto > risco de HipoA
- Cada aumento de 1 mg/kg baixo impacto no risco HipoA
- Uso SID > risco

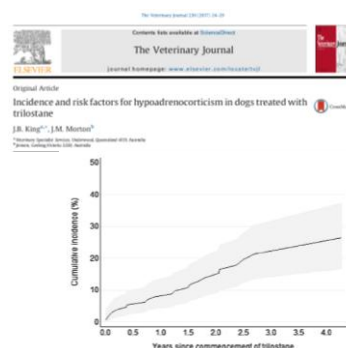
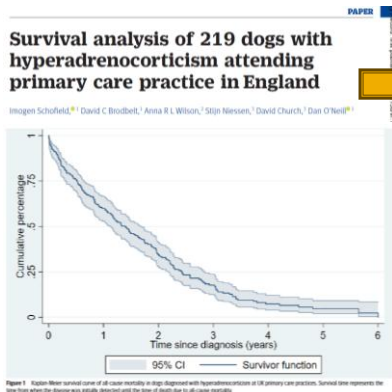


Fig. 1. Cumulative incidences of hypoadrenocorticism by time from commencement of trilostane treatment for 156 dogs with confirmed hyperadrenocorticism. The shaded band indicates the 95% point-wise confidence interval. Estimates were made at each time that a dog was first diagnosed with hyperadrenocorticism. Linear interpolation was used between estimates.

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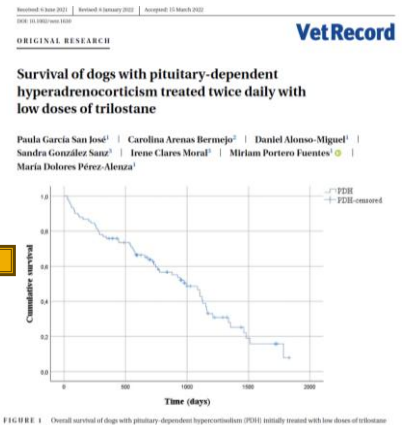
O que Aprendemos com o Tempo sobre o Tratamento com Trilostano?

- Sobrevida é melhor quando empregado em doses menores e com a dose dividida 2x ao dia (ou mais...)



Mediana = 510 (IC95% 412-618 dias)
Dose Inicial = 3,3 ± 1,28 mg/kg/dia

Mediana = 998 (IC95% 775-1128 dias)
Dose Inicial = 0,2 a 1,1 mg/kg q12h

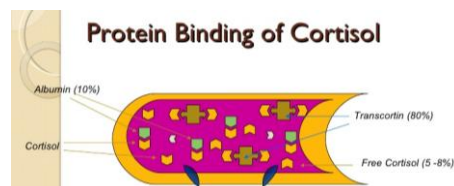


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TRILOSTANO / complicações

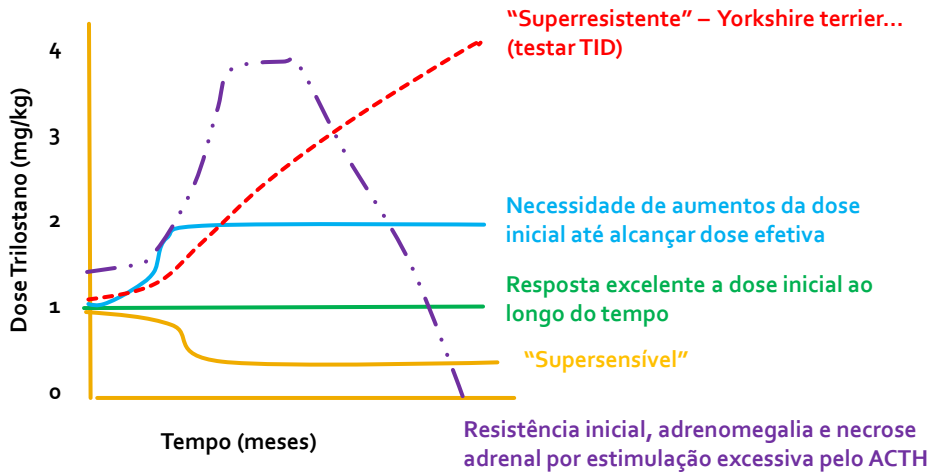
- Bem tolerado na maioria dos casos (anorexia, êmese, diarreia)
- Hipercalemia
- Hipoadrenocortismo,
- Necrose Aguda Adrenal
- Adrenomegalia
- Falta de resposta clínica apesar de um bom valor cortisol pós-ACTH - Hipóteses:

1. Escape adrenal secundário à adrenomegalia e aumento do ACTH?
2. Elevação de precursores?
3. Cortisol livre?



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Padrões de Respostas ao Trilostano



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ADRENALECTOMIA NO HAD

- Recomendada para cães com tumores adrenais funcionais
- Idealmente, iniciar terapia médica com trilostano 1mg/kg BID até controle clínico e hormonal
- Suspende trilostano 24-48h antes da cirurgia

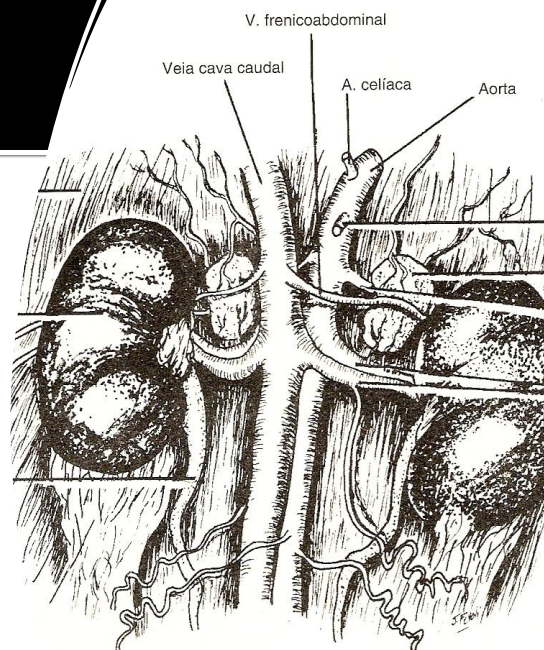


Figura 1: Adrenalectomia por meio de uma abordagem na linha média ventral.

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Fatores Complicadores da Adrenalectomia



Adrenalectomia laparoscópica no tratamento cirúrgico do hiperadrenocorticism em cães: um desafio para a medicina veterinária

Hiperadrenocorticism surgical treatment by laparoscopic adrenalectomy in dogs: a challenge for veterinary medicine

Alan Gomes Pággel - Médico Veterinário, Especialização em Residência (R1) em Clínica e Cirurgia de Pequenos Animais - HCU/UFPRGS, Mestre em Ciências Biológicas - Fisiologia - Laboratório de Metabolismo e Endocrinologia Comparada - ICBS - UFRGS, Colaborador em Nível de Extensão pelo Hospital de Clínica Veterinária da UFRGS - Atendimento de Endocrinopatias

Pággel AG. *Revista Científica de Medicina Veterinária - Pequenos Animais e Animais de Estimação* 2009; 7(20): 37-43.

frontiers | Frontiers in Veterinary Science

TYPE Original Research
PUBLISHED 02 August 2023
DOI 10.3389/fvets.2023.1234567

Laparoscopic vs. open adrenalectomy: perioperative data and survival analysis in 70 dogs with an adrenal tumor

Kirsten L. van Bokhorst^{1,2}, Sara Galac¹, Hans S. Koolstra¹, Janny C. de Graauw^{1,3}, Erik Teske¹, Guy C. M. Grimw¹ and Sebastian A. van Nieuwenhuizen^{1*}



FIGURE 1
Operation room setting during bilateral laparoscopic adrenalectomy through flank approach in sternal recumbency in an Australian Shepherd dog with HC. In the picture, right LA is in progress and left LA has been completed (with 3 portals sutured). Both procedures are performed consecutively without repositioning or re-draping the patient.

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Adrenalectomia

Objective Review medical records of dogs that underwent adrenalectomy without pre-operative medical management, to examine the peri-operative morbidity and mortality.

Design Case series of 65 dogs.

Methods Medical records were reviewed. Features recorded included the histologic diagnosis, intra-operative hypertension or tachycardia, requirement for cavotomy, administration of intra- and post-operative corticosteroids, performance of additional surgery and the occurrence of peri-operative complications. Dogs requiring emergency surgery were excluded.

Results Of the 65 dogs, 49 had adrenocortical tumours (11 bilateral), 13 had pheochromocytomas (one bilateral) and three dogs had tumours in both adrenal glands of a different tumour type. Five dogs had caudal vena cava invasion and 33 had additional procedures performed at the same time. Mortality occurred in 1/65 dogs (1.5%; 95% CI 0.03%–8.2%), major complications were identified in 1/65 dogs (1.5%; 95% CI 0.03%–8.2%) and minor complications occurred in 10/53 dogs (15%; 95% CI 8.6%–26%).

Conclusion Based on the limited peri-operative complications and low mortality in this pre-operatively untreated cohort, and based on critique of the available literature, the added value afforded by pre-operative treatment is questioned. With appropriate management, adrenal tumours can be removed with few peri-operative complications and low mortality.

Keywords adrenalectomy; pre-treatment

Aust Vet J 2020

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AUSTRALIAN
VETERINARY
JOURNAL



AUSTRALIA'S
PREMIER VETERINARY
SCIENCE TEXT



SMALL ANIMALS

ORIGINAL ARTICLE

Short-term outcome of adrenalectomy in dogs with adrenal gland tumours that did not receive pre-operative medical management

C Appelgrein,* G Hosgood, E Drynan and A Nesbitt

Table 1. Tumour type and factors evaluated for an effect on major complications

	Coagulation status (pre-operatively)	Intra-operative blood pressure	Intra-operative heart rate†	Complications
Adrenocortical carcinoma (23 dogs)	Hypocoagulable – 5 Hypercoagulable – 3 Normal – 8	Hypertension – 3 Hypotension – 6	Tachycardia – 2 Bradycardia – 6	Mortality – 0 Major – 1 Minor – 5
Adrenocortical adenoma (26 dogs)	Hypercoagulable – 5 Normal – 9	Hypertension – 2 Hypotension – 6	Tachycardia – 3 Bradycardia – 4	Mortality – 0 Major – 0 Minor – 1
Pheochromocytoma (13 dogs)	Hypocoagulable – 2 Normal – 6	Hypertension – 3 Hypotension – 10	Tachycardia – 5 Bradycardia – 4	Mortality – 1 Major – 0 Minor – 1
Both tumour types (3 dogs)	Not tested	Hypertension – 2 Hypotension – 3	Tachycardia – 1 Bradycardia – 1	Mortality – 0 Major – 0 Minor – 3

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Acesso pela Linha Média (Incisão Paracostal Opcional)

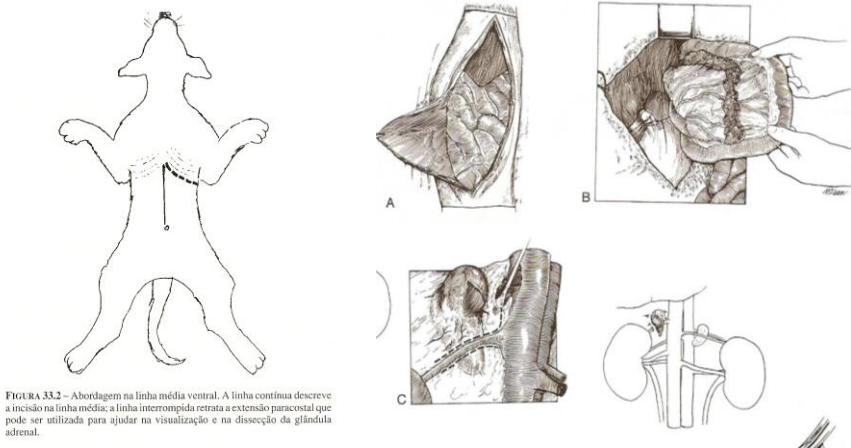
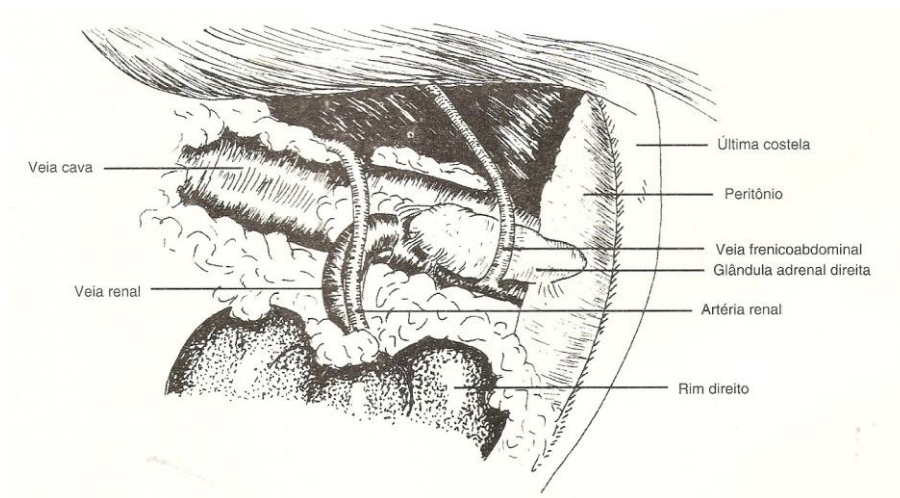


FIGURA 33.3 – Abordagem na linha média ventral. A linha contínua descreve a incisão na linha média; a linha interrompida retrata a extensão paracostal que pode ser utilizada para ajudar na visualização e na dissecação da glândula adrenal.

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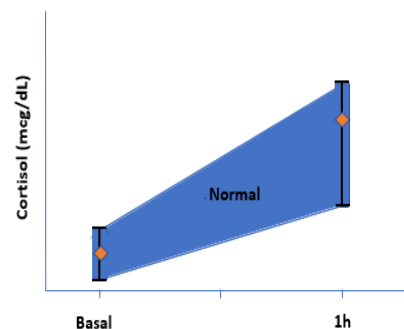
Incisão pelo Flanco e Acesso ao Espaço Retro-peritoneal



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Suplementação Corticoides na Adrenalectomia

- 0,05 a 0,1 mg/kg dexametasona IV quando começar adrenalectomia
- 0,05 – 0,1 mg/kg SC adicionais ao fim do procedimento + 0,1 mg/kg SC após 12 horas
- **Realizar teste de estimulação por ACTH (basal e pós-ACTH)**
- 0,1mg/kg dexta SC cada 12 horas até conseguir começar com prednisona 0,2-1 mg/kg/dia (qto maior o cão menor dose)
- Início da Pred quando retomar apetite e alimentação (normalmente em menos de 24 horas)
- **Redução gradual da prednisona ao longo de semanas (2-4) a meses (1-2) → quanto menor resposta no teste de estimulação maior tempo necessário de desmame.**

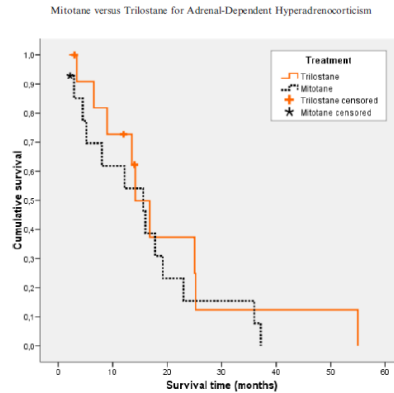


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Long-Term Survival of Dogs with Adrenal-Dependent Hyperadrenocorticism: A Comparison between Mitotane and Twice Daily Trilostane Treatment

C. Arenas, C. Melián, and M.D. Pérez-Alenza

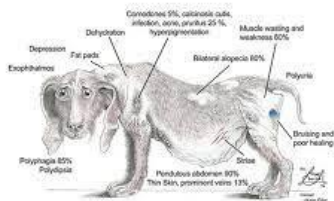
Conclusion and Clinical Importance: The type of medical treatment (mitotane versus trilostane) does not influence survival time in dogs with ADH; therefore, trilostane, a drug with less frequent and milder adverse effects, might be used as the primary medical treatment when adrenalectomy cannot be performed.



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Síndrome de Cushing IATROGÊNICA

- Inibição do eixo secundário a glicocorticoidoterapia crônica...



👤: "A senhora ainda está dando corticoide por conta, né?"
 🐶: "Só as vezes.... quando ele coça."



👤👤: "Vocês não podem ficar dando corticoide por conta!"

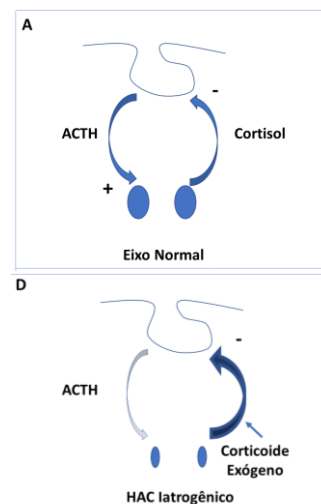


- Desmame gradual para evitar crise Addisoniana (vômitos, náusea, hiporexia, diarreia, prostração, hipotensão, hipoglicemia...)

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Síndrome de Cushing IATROGÊNICA

- **Independente de qual glicocorticoide estava sendo usado, via de administração, ou tempo de tratamento:**
- Reduzir para doses fisiológicas de prednisona/prednisonolona (0,2-0,5 mg/kg) por 5-7 dias
- Se tolerar bem, passar para dias alternados..
- Se tolerar bem, passar para cd 3 dias antes de suspender



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Boretta et al. BMC Veterinary Research (2025) 21:480
https://doi.org/10.1186/s12917-025-04876-9

BMC Veterinary Research

RESEARCH

Open Access

Effects of long-term high-dose prednisolone in Beagle dogs on structural and functional responses of the HPA Axis

Felicitas S. Boretta¹, Livia Harburger¹, Barbara Riond², Elisabeth Neubert¹, Regina Hofmann-Lehmann², Stefan Unterer¹, Matthias Dennler³ and Nadja S. Sieber-Ruckstuhl^{1*}

Abstract

Background Long-term glucocorticoid administration can suppress the hypothalamic-pituitary-adrenal (HPA) axis, increasing the risk of adrenal insufficiency upon withdrawal, with an unpredictable recovery timeline. This study provides a standardized evaluation of a >200-day prednisolone administration regimen in dogs by assessing its effect on HPA axis through adrenocorticotropic hormone (ACTH) stimulation tests, ACTH dynamics monitoring, and adrenal ultrasonography. Four healthy Beagle dogs received once-daily oral prednisolone from days 1–181 (median dose: 2 mg/kg for days 1–150; median dose: 0.25 mg/kg for days 151–181). From days 182–208, prednisolone (median dose: 0.25 mg/kg) was given on alternate days before discontinuation on day 209.

Results All dogs developed clinical signs of hypercortisolism after 150 days of high-dose prednisolone administration. The ACTH stimulation test indicated a reduced cortisol response after 150 days of high-dose administration, though only one dog exhibited cortisol levels below 138 nmol/L. Unexpectedly, endogenous ACTH concentrations were significantly increased on day 150 but had returned to baseline levels by day 183. ACTH curves showed a short-lived suppression, with levels declining within 6 h of each prednisolone dose and rebounding to baseline by 12 h. Ultrasonography revealed significant adrenal downsizing by day 150, with a reduction in the maximal diameter of the caudal pole of both adrenal glands (left: 15–42%, right: 13–26%). By day 211, adrenal size had significantly re-increased compared to day 150.

Conclusions Prolonged, once-daily high-dose prednisolone administration caused overt clinical hypercortisolism and pronounced adrenal shrinkage in dogs; however, most retained a normal functional reserve despite these structural changes. The rapid normalization of ACTH and only mild reduction in cortisol responsiveness indicate that once-daily dosing may allow sufficient off-drug intervals to maintain near-intact HPA function. Nevertheless, the absence of a twice-daily comparison group limits any definitive conclusions about the role of dosing frequency in preventing severe HPA axis suppression.

Keywords Glucocorticoid therapy, Endocrine suppression, ACTH stimulation test, Adrenal atrophy, Canine

SÍNDROME DE CUSHING IATROGÊNICA

- ❖ **Independente de qual glicocorticoide estava sendo usado, via de administração, ou tempo de tratamento:**
- ❖ Reduzir para doses fisiológicas de prednisona/prednisonolona (0,25 mg/kg)
- ❖ Reduzir dose em 25% a cada semana
- ❖ Passar para dias alternados antes interromper

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Obrigado pela
Atenção!

