European Zycortal Symposium

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Welcome

Welcome to the European Zycortal Symposium Proceedings. Zycortal®, launched in April 2016, is Europe's first veterinary licensed injectable treatment for canine hypoadrenocorticism, or Addison's disease.

Addison's disease is one of the more intriguing endocrine diseases, often affectionately called the 'great pretender' due to its vague and sometimes misleading presentation in its chronic form. This only serves to make it all the more satisfying to identify, diagnose and successfully treat.

We are delighted to have attracted internationally renowned speakers to this event to present their experiences and findings, covering the clinical presentation, diagnostic work-up and treatment of canine Addison's disease with Zycortal.

The Proceedings are the result of many hours of thought and work by the authors and organisers. We hope you find the information interesting, relevant, and useful in practice.

Greg Williams
Senior Business Manager (Endocrinology)
Dechra Veterinary Products

Speaker Biographies

Ian Ramsey BVSc PhD DSAM DipECVIM-CA FHEA FRCVS

Ian Ramsey is the Professor of Small Animal Medicine at Glasgow University Veterinary School and editor of the British Small Animal Veterinary Association's (BSAVA) Canine and Feline Animal Formulary. He graduated from Liverpool in 1990, completed his PhD at Glasgow on feline leukaemia virus in 1993 and his residency at Cambridge in 1997. He is a British (RCVS) and European diplomate in small animal medicine.

Ian has written and co-authored nearly 100 scientific papers, review articles and book chapters in various aspects of small animal medicine but his main interest is in endocrinology. He was awarded the BSAVA Woodrow Award for contributions to small animal medicine in 2015 and became a Fellow of the Royal College of Veterinary Surgeons and Honorary Secretary of the BSAVA in 2016.

Away from work he enjoys mountain walking, cycling and classical music.

Nadja Sieber-Ruckstuhl Dipl. ECVIM-CA, Dipl. ACVIM

Current position

Assistant Professor at the Clinic for Small Animal Internal Medicine, Vetsuisse Faculty, University of Zurich, Dipl. ECVIM-CA, Dipl. ACVIM

Education

Since 2014	Assistant professor at the Clinic for Small Animal Internal Medicine, Vetsuisse Faculty University of Zurich
Since 2004	"Oberärztin" at the Clinic for Small Animal Internal Medicine, Vetsuisse Faculty University of Zurich
2002-2003	Visiting Internal Medicine Resident at the Animal Teaching Hospital, University of Georgia, USA
2001-2004	Residency at the Clinic for Small Animal Internal Medicine, Vetsuisse faculty, University of Zurich
2000-2001	Internship at the Clinic for Small Animal Internal Medicine, Vetsuisse faculty, University of Zurich
1999-2000	Doctoral Thesis: DNA-Vaccination against FeLV with IL-12 as adjuvant. Mentor: Prof. Dr. H. Lutz, Clinical Laboratory, Vetsuisse Faculty University of Zurich
1998	School of Veterinary Medicine, Vetsuisse Faculty University of Zurich

Patty Lathan VMD MS DACVIM (Small Animal Internal Medicine)

Patty Lathan attended college at Texas A&M University, veterinary school at the University of Pennsylvania, completed an internship at Mississippi State University, and finished a small animal internal medicine residency at Purdue University in 2007. She is boarded by the ACVIM and is an associate professor of small animal internal medicine at Mississippi State University.

Patty's primary interest is endocrinology, specifically the management of adrenal disease and diabetes mellitus. She has published several articles and book chapters, and currently serves as the President of the Society for Comparative Endocrinology.

Alisdair Boag BSc BVetMed PhD MRCVS

Alisdair Boag graduated from the Royal Veterinary College, University of London after completing an intercalated BSc (Hons) in Immunology and Pathology at King's College, University of London. He then enjoyed working in small animal practice in Derbyshire, before heading to Tufts University, Massachusetts, USA to complete his Small Animal Internship.

Following a return to small animal practice, Alisdair completed a BBSRC CASE sponsored PhD at the Royal Veterinary College, London, with Dechra as an industrial partner. His PhD "An Immunological and Genetic Investigation of Canine Hypoadrenocorticism (Addison's Disease)" was completed in 2014. There followed a move to the Royal (Dick) School of Veterinary Studies, Edinburgh where he is currently a Senior Clinical Training Scholar in Small Animal Internal Medicine.

Alisdair's main clinical and research interests are focussed on canine and feline metabolism and endocrinology.

Eilidh Gunn BVMS DVMS DipECVIM-CA MRCVS

Eilidh Gunn graduated from the University of Glasgow in 2008 before joining a small animal practice in Yorkshire for three years. She then returned to the University of Glasgow's Small Animal Hospital to complete a small animal rotating internship. Following this Eilidh went on to a four-year combined residency and professional doctorate program at the University College of Dublin, during which time she became a European diplomat in internal medicine.

For her professional doctorate, Eilidh focussed on selected aspects of adrenal disease and is particularly interested in the acute management of adrenal crises, and in calcium balance in dogs with hyperadrenocorticism.

Eilidh returned to the University of Glasgow as a clinician in internal medicine in August 2016 and enjoys all aspects of small animal internal medicine, but is particularly interested in endocrinology, medical neurology and feline medicine.

Dan Rosenberg DVM PhD

Dan Rosenberg has been a member of the European Society of Veterinary Endocrinology since its creation and was president of the society from 2011 to 2013. He has been involved over eighteen years in the Internal Medicine Unit of Alfort National Veterinary School in Maisons-Alfort, France. There he created a consultation exclusively dedicated to endocrine disease in companion animals.

In 2013, Dan left 'Alfort School' to participate to the creation of a multidisciplinary referral centre (Micen Vet, Créteil, France). He is author and co-author of diverse research papers, book chapters and books focusing on endocrinology in humans, dogs and cats.

Using Zycortal 5 golden rules:

1

Manage client expectations at the beginning

a) It may take several visits and multiple monitoring blood tests to find the right dose of Zycortal and a glucocorticoid for each dog. This is also true for dogs previously receiving fludrocortisone therapy

b) Dogs being treated properly should be happy dogs with a normal appetite. However it is important to remember that they are not normal dogs. They have a chronic disease and will need lifelong medication and monitoring

c) Owners should understand that the dose of Zycortal is adjusted by assessing electrolytes and clinical signs, whereas the glucocorticoid (mainly in the form of prednisolone) dose is adjusted according to the clinical history (so their observations matter)

2

All dogs must receive daily glucocorticoid treatment titrated to effect based on clinical signs

a) Glucocorticoid deficiency causes lethargy (which can be severe), inappetance, weakness and gastrointestinal signs

b) Equally too much glucocorticoid causes polyuria/polydipsia, poor hair regrowth and increased bodyweight. Remember too much Zycortal can also cause polyuria/polydipsia

c) The starting prednisolone dose rate is 0.2-0.4 mg/kg q24h for newly diagnosed cases. The final dose varies between individual animals and a good proportion of dogs will ultimately be stable at 0.05-0.1 mg/kg q24h. For dogs requiring particularly small doses of glucocorticoid, cortisone acetate could be considered as an alternative

d) Glucocorticoid dose adjustments should be 25 to 50% of the previous dose. Try to wait two weeks to assess the effect

e) At times of metabolic stress or illness, the glucocorticoid dose may need to be increased (2 to 4 times)

3

Use a Zycortal dosing interval of either every 4 weeks, or every month: give a dose appropriate to that interval

a) The preferred approach of EU & US endocrinologists is to adjust the dose and keep the interval constant, rather than adjusting the interval and keeping the dose constant

b) The initial Zycortal dose is 2.2 mg/kg subcutaneously. Should a dose change be required, it is more likely that dogs will require a dose reduction than a dose increase

c) A benefit of a four weekly or a monthly interval is the ease, both for the vet and the client, in booking repeat appointments

4

Evaluate Zycortal treatment success at days 10 and 28 after every dose, until stable

a) Decide if you are giving too much or too little Zycortal to each dog by assessing electrolytes and clinical signs

b) Aim to keep potassium and sodium within their reference ranges (RRs) throughout the dosing interval

c) Adjust the Zycortal dose at day 28 in 10-20% steps with the aim of achieving electrolytes within their RRs at day 10 and day 28
   i) Monitoring electrolytes at day 10 enables assessment of the peak effect of the dose
   ii) Monitoring electrolytes at day 28 enables assessment of the duration of the dose

d) Electrolytes should be within their RRs before administering a repeat Zycortal dose
   i) If potassium is below and/or sodium is above their RRs at day 28:
      (1) Do not inject Zycortal, even at a lower dose
      (2) Repeat electrolyte testing every 7 days until they are within their RRs
      (3) Then re-inject Zycortal at a lower dose and recheck at day 10 and day 28 post-injection
   ii) If potassium is above and/or sodium is below their RRs at day 28 Zycortal must be injected. The dose should be increased, and/or the dose interval shortened

e) Once the dose has been determined, a stable dog will have electrolytes within their respective RRs at days 10 and 28 during at least two consecutive treatment cycles using that same dose. Thereafter dogs should be reassessed every 4-6 months at the time of injection.

f) In cases of lack of expected efficacy; before increasing the Zycortal dose, consider whether the dog was adequately hydrated at injection, the product was adequately re-suspended, and whether the injection was successfully administered

5

If you have problems then get help

a) Check laboratory results that do not look right. e.g. contamination of the sample with potassium EDTA from a haematology tube can cause an artefactual increase in serum potassium

b) If a dog receiving Zycortal therapy is ill:

   i) Giving more glucocorticoid is rarely wrong
   ii) Consider potassium supplementation if the dog is symptomatic and potassium <3 mmol/l.

c) Contact Dechra Technical Services for support regarding individual cases

Aetiology of Addison's disease

Alisdair Boag, BSc BVetMed PhD MRCVS

A brief historical perspective of Addison's disease

Thomas Addison first made the connection between a previously idiopathic form of anaemia which "makes its approach in so slow and insidious a manner, that the patient can hardly fix a date to his earliest feeling of that languor, which is shortly to become so extreme" and adrenal gland pathology in a talk to the South London Medical Society in 1849.[1,2] This initial report was followed in 1855 by his seminal work "On the Constitutional and Local Effects of Disease of the Suprarenal Capsules", a case series, including post mortem examinations, of 11 patients whose disease was characterised by anaemia and skin discolouration in addition to a range of adrenal pathology.[2,3] Prompted by Addison's observations, a series of adrenalectomy experiments were performed in several species, including dogs, which led to death of the animal, establishing the importance of the adrenal gland for life.[4]

Whilst the physiological role of the adrenal glands was not known,[5] the potential for cortical extracts to prolong life was first robustly demonstrated in dogs, in a series of adrenalectomy experiments entitled "Studies on Adrenal Insufficiency in Dogs".[6] These and other papers provide very clear descriptions of familiar clinical features of hypoadrenocorticism in dogs, including inappetence, weakness and vomiting.[6,7] Furthermore, increased urine sodium excretion and decreased potassium excretion, leading to hypernatraemia and hyperkalaemia[7-9] were also noted decades before the first spontaneous cases were reported.

That dogs suffer recognisable signs and physiologic changes post-adrenalectomy emphasises that Addison's disease, as a syndromic diagnosis, is not necessarily a consequence of one aetiology contributing to one specific pathology. Instead, Addison's disease is due to a lack of functioning adrenal tissue and therefore can have a range of aetiologies and subsequent pathologies.

It is worth noting that although Addison's original case series consisted primarily of people who had suffered tuberculosis (TB) with adrenal gland infiltration destroying the gland, one case almost certainly represents the first description of autoimmune Addison's disease; the most common cause of Addison's disease in developed countries. Addison's post mortem findings include the following description:

"The two supra-renal capsules together weighed 49 grains; they appeared exceedingly small and atrophied; the right one was natural, firm; the left deformed by contraction; each adherent to surrounding parts by dense areolar tissue. The section gave a pale and homogeneous aspect; it presented a fibrous tissue, fat and cells about the size of white blood-corpuscles."

More remarkably, given knowledge at the time, were Addison's reflections on this pathology:

"It is, moreover, of some significance and importance to observe, that in the present instance, the diseased condition of the supra-renal capsules did not result as usual from a deposit either of a strumous or malignant character, but appears rather to have been occasioned by an actual inflammation,- that inflammation having destroyed the integrity of the organs, and finally led to their contraction and atrophy."

Most common pathogenesis and aetiology in humans and dogs

In humans the pathology of Addison's disease has changed over time, historically tuberculosis was the most frequent cause of adrenal failure, but more recently an autoimmune pathogenesis has become more prevalent in developed countries.[3,10] In one study, 91% of Addisonian patients had an immune-mediated pathology,[11] though a range of aetiologies and pathologies have been described.[10]

In humans, the most common aetiology underlying the immune mediated pathology is due to complex genetic predispositions, with several susceptibility genes and additional environmental factors each contributing to disease.[12] The general increased genetic predisposition to autoimmunity is exemplified by the increased prevalence of Addison's disease, coeliac disease, lymphocytic thyroiditis, pernicious anaemia, ulcerative colitis, SLE and rheumatoid arthritis in parents of children with Type 1 Diabetes;[13] this may be similar to breeds of dog which are over-represented for several immune mediated conditions. Large scale genome-wide association studies have been undertaken to better understand the genetic basis of human autoimmune endocrinopathies, with similar genes identified as playing a role in several conditions.[14]
The major susceptibility locus associated with immune-mediated endocrinopathies, including immune mediated Addison's disease, is the major histocompatibility complex (MHC).[15]
Two other genes have been consistently shown to be involved in a range of autoimmune diseases, protein tyrosine phosphatase, non-receptor 22 (PTPN22), which is involved in intracellular T cell receptor signalling[16,17] and cytotoxic T-lymphocyte-associated protein 4 (CTLA4),[17,18] an important regulator of T cell activation. Associations with other genes have also been described for immune mediated Addison's disease including, MIC-A and MIC-B,[19,20] BACH2,[21] IL-2,[22] Vitamin D receptor[23] and CYP27B1.[24,25]

In dogs, the pathology appears to mirror that seen in the majority of humans. The first histopathological descriptions of canine Addison's disease were consistent with an immune-mediated pathology, with small adrenal glands containing minimal medullary change and selective destruction of the cortex with lymphocyte and plasma cell infiltrate present in two dogs and lymphocytes "diffusely infiltrated through the cortical remnant" in the third case described.[26] Further case reports and case series have indicated that a lymphocytic adrenalitis is present, followed by atrophy in end-stage disease.[27-31] Further evidence of immune mediated pathogenesis comes from the presence of autoantibodies, regarded as an important indicator of autoimmune disease.[32-34] Autoantibodies in human patients have long been recognised.[35] Circulating autoantibodies targeting 21-hydroxylase (21-OH) are present in 90% of human patients at diagnosis and in approximately 50% of patients with longer standing disease.[17,36,37]

A case report of Addison's in a dog with evidence of serum 21-OH autoantibodies has been recently published,[38] although 21-OH autoantibodies were not identified in a larger cohort of affected dogs.[39] Antibodies against the cytochrome P450 side-chain cleavage enzyme (P450scc) have been described in a cross-section of 24% of dogs affected with hypoadrenocorticism.[39]

Assessing the underlying genetic predispositions as aetiology for an autoimmune pathogenesis for canine hypoadrenocorticism has been performed with susceptibility linked to immune response genes including MHC class II, CTLA4 and PTPN22 across multiple breeds.[40-46]

Uncommon and rare aetiologies

Whilst still producing an immune-mediated phenotype, recently a subset of Nova Scotia Duck Tolling Retrievers (NSDTRs) in the USA have been identified as suffering a monogenic disorder leading to 75% of homozygous dogs developing hypoadrenocorticism before one year of age, termed Juvenile Addison's Disease (JADD). Around 25% of these dogs suffer concurrent autoimmune disease and have a markedly reduced life expectancy.

In humans, autoimmune polyglandular syndrome type 1 is a rare disease, occurring in around 1 in 80,000 people,[10] the genetic basis of this syndrome has been identified as mutations in the autoimmune regulator (AIRE) gene. AIRE is a transcription factor that regulates expression of tissue-specific antigens by thymic epithelial cells,[47] disruption of the AIRE gene alters the profile of self-antigens presented in the thymus and subsequently autoreactive T cells migrate into the periphery.[48] A missense mutation in the AIRE gene has been found to be associated with hypoadrenocorticism in Border Collies.[41] Although further work is required to better characterise the biological significance of this association, this raises the possibility that mutations in the canine AIRE gene might be involved in susceptibility to autoimmune disease in some dog breeds.

As a non-immune mediated pathology, congenital adrenal hyperplasia (CAH) is the most common form of Addison's disease diagnosed in children less than two years of age;[49] it is caused by mutation(s) in enzymes of the steroid synthesis pathway. Mutations affecting CYP21A2 (21-hydroxylase; 21-OH) account for over 90% of affected individuals.[50] A single nucleotide polymorphism (SNP) in CYP21A2 associated with susceptibility to hypoadrenocorticism has been described in West Highland White Terriers (WHWTs), though further investigations are needed to confirm this link.[41]

Other non-autoimmune causes of primary hypoadrenocorticism include neoplastic infiltration of the adrenal glands,[51,52] infiltration with histoplasmosis[31] and bilateral abscessation.[53]

In dogs, secondary Addison's, caused by a lack of ACTH production from the pituitary gland, makes up a much smaller number of cases than primary Addison's disease, with estimates of around 2-4% in referral populations.[54,55] Reports of causes of secondary hypoadrenocorticism include head trauma[56,57] and withdrawal of steroid administration,[58,59] however in most reports the underlying cause is not identified;[54,55,60] in humans an immune-mediated pathogenesis has been hypothesised as a cause of secondary Addison's disease.[61]

Hypoadrenocorticism is a heterogeneous disease, and although a lack of glucocorticoid production is a consistent feature, the aetiology and pathogenesis of disease in an individual animal or in individual breeds of dogs are not well investigated. The evidence from epidemiologic

studies highlights breed-specific predispositions, and results of inheritance studies and molecular genetic studies allow a genetic basis of disease to be inferred. It is clear that there is a great degree of overlap in underlying genetic risk factors when comparing breeds and likely between different autoimmune conditions, mirroring the situation in humans. However, the immunologic consequences of inheriting susceptibility genes and the environmental factors that trigger progression of autoimmune disease in genetically susceptible individuals require further research.

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The clinical presentations of Addison's disease

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Introduction

Causes

Hypoadrenocorticism is the term used to describe the failure of glucocorticoid (primarily cortisol) and mineralocorticoid (aldosterone) secretion by the adrenal cortex. Cortisol has many roles within the body, all of which tend to protect the body from metabolic stresses (such as starvation and inflammation). It is important in the maintenance of the normal gastro-intestinal barrier, as a counterbalance to insulin and has a role in the regulation of calcium balance. Aldosterone has a more specific role as a long term regulator of plasma volume which it achieves by controlling the retention of sodium (and excretion of potassium) by the body.

Hypoadrenocorticism may be primary (due to adrenal gland disease) or secondary (due to pituitary problems). The most common form of primary hypoadrenocorticism is an immune mediated destruction of the adrenal cortex. Primary hypoadrenocorticism may also be seen with the use of adrenal-suppressive drugs such as trilostane and mitotane.

Less commonly, cases of primary hypoadrenocorticism may be seen with isolated glucocorticoid deficiency (hypocortisolism) or, very rarely, isolated hyperaldosteronism. Isolated primary hypocortisolism is sometimes referred to as atypical hypoadrenocorticism (but this term is also sometimes (incorrectly) applied to dogs that have typical primary hypoadrenocorticism but have normal electrolyte concentrations). The underlying pathogenesis has not been determined.

Secondary hypoadrenocorticism usually results from the sudden cessation of long term steroid therapy that has been sufficient to cause suppression of adrenocorticotrophic hormone secretion by the pituitary gland. This suppression leads to atrophy of the adrenal cortex such that when the exogenous steroids are withdrawn, acute secondary hypocortisolism results (aldosterone production is nearly always maintained). Spontaneous pituitary failure of ACTH secretion is very rare but can be detected in some dogs with congenital hypopituitarism and pituitary haemorrhage.

Clinical Signs

Hypoadrenocorticism is associated with a range of clinical signs that vary from mild to severe, fluctuating to persistent and from acute to chronic. It is easy to miss cases. Clinicians should expect the unexpected with hypoadrenocorticism – and yet cannot perform ACTH stimulation tests on every case. This can make recognition of the condition challenging and it is therefore important to include hypoadrenocorticism as a potential differential diagnosis of numerous non-specific signs. The common and not so common clinical signs are summarised in Table 1 (below).

Common	**Lethargy** **Anorexia** **Vomiting** **Poor peripheral pulses**	**Weakness** **Collapse** **Poor body condition** **Shock**
Uncommon	**Diarrhoea** **GI haemorrhage** **Weight loss** **Seizures**	**Abdominal pain** **PU/PD** **Muscle cramps** **Regurgitation**

The historical findings may be vague, such as weight loss, lethargy and inappetence, or they may be more specific e.g. chronic gastrointestinal signs such as abdominal pain, melena or haematochezia or neurological abnormalities (episodic collapse). It is easy to confuse hypoadrenocorticism with other conditions. Physical examination findings can be as variable as the history and, unless the patient has been presented in a state of collapse, there are often no significant findings on examination.

All of the clinical signs can respond to treatment with fluids (and/or steroids), and some will appear to respond to other treatments because of the relapsing nature of the condition. A significant minority of patients can present following acute collapse with no previously noted clinical signs, however the majority have a longer history on closer questioning of the owner.

There are no clinical signs that can be considered truly pathognomic however there are a few findings that can significantly increase the clinician's suspicion of disease:

- Bradycardia or a normal heart rate despite findings of hypovolemia.
- More severe hypovolemia than would be expected from the fluid losses (vomiting and diarrhoea) reported.
- Poor body condition despite only a recent history of disease.

Routine Laboratory Tests

Haematology

The most common haematological finding in dogs that have hypoadrenocorticism is the absence of a stress leukogram (which can be seen in up to 92% of patients with hypoadrenocorticism). Another common finding is a non-regenerative anaemia (normocytic normochromic) which can be seen in up to 25% of patients. This is due to a reduced red blood cell production but may be compounded by gastrointestinal blood losses. Less commonly a patient may present with an increased PCV due to hypovolaemia and haemoconcentration. An absolute lymphocytosis is only seen in 10% of cases, whereas eosinophilia is seen in 20% (Scott-Moncrieff 2015). The 'classical' reverse stress leukogram (low to normal neutrophil numbers with an increase in lymphocytes and eosinophils) is very unusual. As with clinical signs, haematological findings can be completely normal. There are a couple of descriptions of using ratios of white blood cell parameters as sensitive diagnostic aids (which are useful to exclude the diagnosis of hypoadrenocorticism), however none are specific enough to rely on to confirm the diagnosis.

Biochemistry

Electrolyte abnormalities (hyperkalaemia and/or hyponatraemia) are the most commonly noted biochemical abnormality in cases of hypoadrenocorticism. The sodium to potassium ratio is rarely helpful and increases the risk of misdiagnosis in cats and dogs. There are several other causes of low sodium to potassium ratios including GI disease, renal disease and a variety of other conditions.

Hypochloraemia and hyperphosphataemia may also be seen. Electrolyte abnormalities are due to mineralocorticoid (aldosterone) deficiency and therefore are not found in dogs with isolated hypocortisolism. Not all dogs with mineralocorticoid deficiency develop electrolyte abnormalities. The reason for this observation is not clear.

Electrolyte abnormalities can correct rapidly following initiation of fluid therapy and so blood samples must be taken before this has been started.

The second most common finding on biochemistry is azotaemia. This is predominantly pre-renal in origin however intestinal blood losses can lead to proportionally higher increases in urea compared to creatinine. Dehydration due to water loss from the kidneys, secondary to aldosterone deficiency, leads to a pre-renal azotaemia. In some cases this may worsen pre-existing renal disease or possibly even cause chronic kidney disease. Azotaemia in patients with hypoadrenocorticism normally corrects within 48 hours of intravenous fluid therapy.

Other findings on biochemistry include hypoglycaemia, hypoalbuminaemia, hypercalcaemia and hypocholesterolaemia. The hypoglycaemia is thought to be due to the reduction in the insulin antagonism of cortisol. The hypoalbuminaemia is thought to be multifactorial with a reduction in appetite, gastro-intestinal malfunction and haemorrhage all being involved. Hypocholesterolaemia is linked to a reduction in fat absorption which is known to occur. The cause of the hypercalcaemia remains unknown despite investigation (Gow and others).

Urinalysis

Even though patients with hypoadrenocorticism often present with hypovolemia and pre-renal azotaemia, their urine specific gravity rarely exceeds 1.025. This can make differentiation from azotaemia due to renal insufficiency (e.g. due to chronic kidney disease, CKD) difficult but patients with CKD rarely present with hyperkalaemia or hyponatraemia. Acute kidney injury (AKI) however, can cause similar electrolyte changes to hypoadrenocorticism and therefore clinicians can often be faced with the challenge of distinguishing AKI from hypoadrenocorticism. Patients with AKI frequently are anuric or have reduced renal output. In addition, patients with AKI usually have a stress leukogram (increase in neutrophils) and are rarely anaemic. If initial laboratory tests still fail to distinguish AKI patients from patients with hypoadrenocorticism, then response to treatment and clinical progression can be monitored. Diagnostic tests should always be performed prior to starting fluid therapy.

Common	**Hypoalbuminaemia** **Hypercalcaemia** **Non-regenerative anaemia** **No stress leucogram** **Hyponatraemia** **Hyperkalaemia** **Azotaemia** **Minimally concentrated urine (USG < 1.030)**
Uncommon	**Hypoglycaemia** **Neutropenia** **Lymphocytosis** **Eosinophilia** **Hypocholesterolaemia** **Isosthenuric urine (USG < 1.015)**

Diagnostic Imaging

Radiography

Abdominal radiography is not used in the diagnosis of hypoadrenocorticism, however it is sometimes indicated to investigate differential diagnoses such as obstructive gastrointestinal disease. Thoracic radiographs can be useful as the presence of microcardia and reduction in pulmonary vessel diameter can be suggestive of hypovolaemia. Rarely, megaoesophagus is seen as an anecdotal complication in patients with hypoadrenocorticism. However, the authors do not routinely radiograph patients in which hypoadrenocorticism is suspected.

Abdominal Ultrasound

This is indicated to rule out other diseases such as kidney disease, pancreatitis, gastrointestinal disease and liver disease, which can all present with similar clinical signs. Ultrasonography also allows assessment of adrenal size when utilised by the skilled clinician. Bilateral reduction in adrenal gland size and, in particular, left adrenal gland thickness less than 3.2mm is highly suggestive of hypoadrenocorticism, although this is not a sensitive test. Previous treatment with steroids can also cause a reduction in adrenal thickness and so reduces the specificity of this test when the clinical history is unknown or includes steroid administration.

Echocardiography

Echocardiography may be performed due to concerns of cardiac function, particularly in bradycardic patients. A basic echocardiogram may subjectively indicate volume underload and demonstrate poor systolic function. It is important that the latter finding is not overinterpreted (e.g. as dilated cardiomyopathy). The changes in hypoadrenocorticism would be expected to improve with treatment.

Electrocardiographic Changes

Patients may be presented with bradycardia and therefore electrocardiography (ECG) may be one of the first tests performed in an emergency. Conduction abnormalities arise because of increases in potassium and reductions in sodium making it more difficult to achieve threshold pacemaker potential. Changes seen range from widened QRS complexes to ectopic ventricular beats, and from low amplitude P waves to complete absence of P waves. Spiked T waves may also be seen. It is important to note that the ECG gives no reliable indication of the plasma potassium levels. This is because the hypercalcaemia can be cardio-protective and acidosis can cause increases in extracellular potassium levels.

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Confirming the diagnosis of Addison's Disease and how to avoid pitfalls in diagnostic workup

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ACTH Stimulation Tests

Despite attempts to identify alternative diagnostics, the gold standard for definitive diagnosis of hypoadrenocorticism is still the ACTH stimulation test. A baseline cortisol sample should be collected, then a dose of 5 µg/kg, up to 250 µg/dog, of tetracosactide (Synacthen®) is given intravenously (intramuscular is not recommended due to questionable absorption in dehydrated and/or hypovolemic patients). One hour post-stimulation cortisol samples of <2 µg/dl (55 nmol/l) are consistent with hypoadrenocorticism. Rarely, cases of secondary hypoadrenocorticism with low ACTH concentrations may have post-stimulation cortisol values up to 3 µg/dl (Peterson et al, JAVMA, 1996).

Some clinicians have questioned whether one hour post-ACTH cortisol concentrations above 2 µg/dl, but below the laboratory's reference range, may represent a subset of dogs with hypoadrenocorticism. Wakayama et al (Vet Record, 2017) evaluated nine dogs with suspected atypical hypoadrenocorticism that had post-ACTH cortisol concentrations ranging between 3.4 and 8.0 µg/dl (94 and 223 nmol/l). In the seven dogs for which follow-up was available, four dogs were eventually diagnosed with inflammatory bowel disease, two dogs had no return of clinical signs following discontinuation of prednisone, and one dog did not respond to glucocorticoid treatment. Thus, this study does not provide evidence for the diagnosis of hypoadrenocorticism in dogs with post-ACTH cortisol concentrations >3 µg/dl (84 nmol/l).

Any glucocorticoids given days prior to the test may blunt the response, and it is not uncommon for a dog with a history of recent glucocorticoid administration to have a post-stimulation cortisol of 2.5–5.0 µg/dl. Even aural glucocorticoids can suppress the axis and result in post-ACTH cortisol concentrations as low as 2 µg/dl (Aniya et al, Vet Derm, 2008). Most synthetic glucocorticoids (including prednisone and methylprednisolone) will interfere with the cortisol assay itself, and may cause a falsely increased cortisol result. However, dexamethasone and triamcinolone do not cross-react with the cortisol assay, and may be given prior to or during the ACTH stimulation test.

Aldosterone-to-Renin and Cortisol-to-ACTH Ratios

Due to the time and expense associated with the ACTH stimulation test, investigators have evaluated alternative methods to diagnose hypoadrenocorticism. One strategy uses the feedback principles of the hypothalamic-pituitary-adrenal axis and the renin-angiotensin-aldosterone system. In normal dogs, aldosterone concentrations should increase in response to high renin (or plasma renin activity) concentrations, and when no aldosterone is present. Thus, a low aldosterone and high renin concentration, resulting in a low aldosterone-to-renin ratio (ARR), is inappropriate in a hypovolemic, hyperkalemic patient. Likewise, ACTH stimulates the release of cortisol in normal dogs, and cortisol feeds back to the pituitary to inhibit further ACTH secretion. In hypoadrenocorticism, lack of negative feedback of cortisol on the pituitary gland results in a decreased cortisol-to-ACTH ratio (CAR).

Javadi et al (JVIM, 2006) were the first group to evaluate the ARR and CAR in dogs. They compared normal dogs with Addisonian dogs, and found that while there was overlap between aldosterone, renin (plasma renin activity), cortisol, and ACTH, there was no overlap between ARR and CAR. Two later studies (Lathan et al, JVIM, 2014 and Boretti et al, JVIM, 2015) compared CAR between normal dogs, dogs with non-adrenal illness (or diseases mimicking Addison's), and dogs with Addison's. There was no overlap between the CAR in dogs with Addison's vs healthy dogs and dogs with non-adrenal illness in the Lathan study, but there was overlap between two dogs with Addison's and dogs in the non-adrenal illness category in the larger Boretti study. No dogs with secondary hypoadrenocorticism were included in the former study, and only one dog in the latter. Thus, no conclusions could be made regarding the CAR in dogs with secondary Addison's. Importantly, even though there was minimal overlap between the CARs of Addisonians and non-Addisonians in all three studies, the ranges for the CARs for each group differed between studies. Due to these inconsistencies, the CAR cannot be recommended for definitive diagnosis of Addison's at this time.

Baseline Cortisol

Although definitive diagnosis of Addison's requires an ACTH stimulation test, the disease can be **ruled out** by evaluating baseline cortisol values. If the baseline cortisol is >2 µg/dl (>55 nmol/l), the dog is very unlikely to have hypoadrenocorticism. If the baseline cortisol is <2 µg/dl (55 nmol/l), or <3 ug/dl with a very high suspicion of disease, an ACTH stimulation test MUST be run to confirm the diagnosis.

A recent study (Gold et al, JVIM 2016) evaluated cut-off values of <2 µg/dl (55 nmol/l) and found that a basal cortisol concentration of <2 µg/dl had a sensitivity of 99.4%, and a concentration <0.19 µg/dl (5.5 nmol/l) had a specificity of 99.1% for the diagnosis of hypoadrenocorticism. The study included 163 dogs with Addison's, and 351 dogs with non-adrenal illness. Three dogs with non-adrenal illness had baseline cortisol concentrations <5.5 nmol/l, meaning that these patients would have been falsely diagnosed with Addison's using that cut-off value alone. Thus, further studies are needed to determine whether other diagnostic criteria may help increase the specificity and eliminate false positives, as inappropriately treating a dog with glucocorticoids and mineralocorticoids for life has significant negative financial and medical consequences.

Redefining 'atypical' Addison's disease

Claudia E. Reusch

History and currently used terms

The term "atypical" hypoadrenocorticism was first introduced into the literature 36 years ago[1]. The authors described three dogs with unspecific clinical signs such as lethargy, anorexia, weight loss, episodic haematochezia and episodic vomiting. The most consistent laboratory findings were non-regenerative anaemia, eosinophilia and azotaemia, the latter was considered to be prerenal. Sodium and potassium concentrations were within normal limits. In all three dogs basal cortisol was low and failed to increase after ACTH leading to the diagnosis of hypoadrenocorticism. Two dogs were treated with daily prednisone/prednisolone and fludrocortisone from the beginning, one dog only received daily prednisolone. The latter dog initially recovered but was returned to the hospital after 15 weeks because of anorexia, lethargy, ataxia and vomiting. At that time the "typical" electrolyte abnormalities (hyponatremia, hyperkalaemia) were present and fludrocortisone was added to the treatment regimen. Another dog revealed hyponatremia during a re-check 14 months after diagnosis which resolved by increasing the fludrocortisone dose. The authors stated that the dogs most likely suffered from primary (and not secondary) hypoadrenocorticism, in particular those two dogs which developed electrolyte abnormalities later in the course of the disease. Although aldosterone was not measured they hypothesised that the initial clinical signs had been caused by glucocorticoid deficiency and that the later development of electrolyte abnormalities indicated the onset of additional aldosterone deficiency. Thereafter, various case reports and small case series describing dogs with hypoadrenocorticism and normal electrolytes were published. Since the study by Rogers et al[1] the terms "atypical" hypoadrenocorticism and "glucocorticoid-deficient hypoadrenocorticism" have been used by various authors interchangeably. A clear definition is still lacking (see also later). Most investigators would certainly agree that the term flags dogs with primary hypoadrenocorticism without hyponatremia and hyperkalaemia. Some authors have used the term "atypical" hypoadrenocorticism for dogs which had normal potassium but low sodium[2], this, however, is not common practice today.

Unfortunately, however, most studies lack thorough work-up. Usually, measurement of endogenous ACTH was not performed and it is, therefore, possible that some of the "atypical" cases in fact suffered from secondary hypoadrenocorticism. Additionally, most of the time only pre- and post-ACTH cortisol concentrations were evaluated and as the electrolytes were normal it was assumed that the zona glomerulosa and the aldosterone secretory capacity were intact. This assumption, however, most likely is incorrect for many cases. Dogs with so called "atypical" hypoadrenocorticism usually have low-undetectable aldosterone concentrations[3,4] (see later). The long-used term "glucocorticoid-deficient hypoadrenocorticism" is therefore misleading.

Clinical signs and laboratory results

Clinical signs are unspecific and include anorexia, weight loss, exercise intolerance, lethargy and gastrointestinal signs such as vomiting and diarrhoea. Diarrhoea may be of small or large bowel origin, with or without blood (haematochezia or melena), may range from mild to severe, may be acute or chronic and may show episodic or a more permanent occurrence. Haematochezia may also be present in dogs with normal stool consistency.[4,5,6,7,8] A recent multi-centre study prospectively evaluated 151 dogs with chronic gastrointestinal signs and demonstrated that 6/151 (4%) suffered from hypoadrenocorticism. All six dogs had normal sodium and potassium concentrations. Unfortunately, as in many other studies, endogenous ACTH was not measured: it remains therefore unknown if some of the cases in fact suffered from secondary hypoadrenocorticism. No historical information or laboratory parameter was able to separate hypoadrenocorticism from other diseases causing chronic GI disease[9]. In rare instances dogs with "atypical" hypoadrenocorticism may have features of protein-losing enteropathy, including ascites and peripheral oedema[7].

Less common signs are polyuria/polydipsia, regurgitation due to megaoesophagus and collapse. The megaoesophagus may be reversible in some but not all of the cases.[10,11,12] Collapse may be due to hypoglycaemia, which may be the presenting clinical problem, but hypoglycaemia has also been reported to only occur after anaesthesia[13]; collapse can also be caused by anaemia due to GI-bleeding[12].

CBC abnormalities include anaemia, which may be severe in case of GI-bleeding, lack of stress leukogram, lymphocytosis and eosinophilia, the latter two are relatively rare findings. Potential biochemical abnormalities are hypoalbuminemia/hypoproteinaemia ranging from mild to very severe, hypocholesterolaemia, hypoglycaemia and azotaemia, the latter is relatively uncommon.[7,8,12,14,15] Sodium and potassium concentrations are within the reference interval. In some cases potassium may even be low, most likely due to anorexia, diarrhoea or pre-treatment with potassium-free fluids.[3,16,17]

Hypercalcaemia is recognised in approximately 30% of dogs with primary hypoadrenocorticism. According to the results of a small study the majority of dogs (5/7) with increased total calcium also have increased ionised calcium[18]. Different to earlier assumptions dogs with "typical" hypoadrenocorticism are not more likely to have increased calcium levels than those with "atypical" disease[19]. It is also possible that dogs reveal a low total calcium, this is usually associated with hypoalbuminaemia/hypoproteinaemia. It should be noted, that laboratory results in "atypical" cases may also be unremarkable or abnormalities may be negligible.

Frequency of 'atypical' hypoadrenocorticism and risk of misdiagnosis

The reported percentage of dogs with hypoadrenocorticism lacking the typical electrolyte abnormalities ranges from quite low to more than 30% (3/23 = 13%[20]; 5/220 = 2.2%[21]; 6/44 = 13.6%[14]; 5/42 = 12%[22]; 24%[15]; 12/36 = 33%[19]). In a group of Nova Scotia Duck Tolling Retrievers 8/25 dogs (36%) and in a group of Soft-Coated Wheaten Terriers 9/82 dogs (11%) with hypoadrenocorticism had normal sodium and potassium concentrations.[23,24] The differences may

probably be explained by different degrees of awareness of “atypical” hypoadrenocorticism among veterinarians, increased awareness during the last years and the fact that in secondary/tertiary referral centres frequency of “atypical” cases is higher than in primary care practices. In our hospital, with approximately 60% referred and 40% primary cases, the percentage of “atypical” hypoadrenocorticism has been around 12% during the last decade. It is very important to note that the risk of false diagnosis is quite high with regard to “atypical” hypoadrenocorticism. In Zurich we currently see more dogs with misdiagnosis than with true “atypical” hypoadrenocorticism. The reason in those cases is treatment with glucocorticoids or progestogens at some time before the ACTH stimulation test. It is very important to recognise the limitations of the ACTH stimulation test. Low cortisol concentrations pre- and post-ACTH do not allow differentiation between primary and secondary hypoadrenocorticism, nor between naturally occurring hypoadrenocorticism and iatrogenic secondary hypoadrenocorticism (suppressed pituitary-adrenal axis due to steroid application). Lack of electrolyte abnormalities is seen in three settings: iatrogenic secondary hypoadrenocorticism, naturally occurring secondary hypoadrenocorticism and “atypical” primary hypoadrenocorticism. Iatrogenic secondary hypoadrenocorticism is by far the most common form. It is, therefore, of utmost importance to exclude prior steroid application in dogs with low pre- and post-ACTH cortisol concentrations. Oral, parenteral and topical steroid administration all lead to suppression of the pituitary-adrenal axis and its duration varies depending on preparation, dose, duration of application and individual glucocorticoid sensitivity.

Comparison between ‘typical’ and ‘atypical’ hypoadrenocorticism

Thompson et al[15] compared clinical data of 35 dogs with “typical” hypoadrenocorticism with those of 11 dogs with “atypical” disease. The latter were a mean of 2.6 years older and had a longer duration of clinical signs (mean 4.4 versus 1.2 months). Most likely, these differences reflect the fact that “atypical” cases may go undetected for longer periods because the clinical signs are non-specific and typical biochemical abnormalities are absent. Vomiting was less common in “atypical” cases and the number of dogs to be in shock on arrival in the hospital was lower (1/11 versus 9/34 dogs). The “atypical” cases were more likely to have anaemia, hypoalbuminemia and hypocholesterolaemia and less likely to be azotaemic, hypercalcaemic and acidotic. None of the “atypical” dogs died in the hospital, whereas 3/35 “typical” dogs died.

Histology of the adrenal gland in dogs with ‘atypical’ hypoadrenocorticism

Normally, all layers of the adrenal cortex are affected in immune-mediated primary hypoadrenocorticism. A logical explanation for “atypical” hypoadrenocorticism would be, that the destructive process in the adrenal gland is limited to the zona fasciculata and zona reticularis (leading to cortisol deficiency) and that the zona glomerulosa is spared, resulting in normal aldosterone secretion. Unfortunately, only very few histological data are available and therefore no definitive conclusion can be drawn.

Kooistra et al[25] described an 8-year-old Boxer with combined primary hypothyroidism and primary “atypical” hypoadrenocorticism (polyglandular deficiency syndrome or Schmidt-

syndrome). Histology of the adrenal glands revealed lymphocytic adrenalitis with complete destruction of the zona fasciculata and zona reticularis while the zona glomerulosa was preserved. Adissu et al[26] reported a case of a 4-year-old Great Pyrenees with hypothyroidism and hypoadrenocorticism with normal sodium and potassium concentrations. Histology revealed almost complete replacement of the zona fasciculata and reticularis by lymphocytes, plasma cells and macrophages, whereas the zona glomerulosa was spared.

Frank et al[27] examined the adrenal glands of 33 dogs with adrenalitis or adrenocortical atrophy by means of histopathology. Three of the dogs had diffuse atrophy of the zona fasciculata and reticularis with segmental sparing of the zona glomerulosa. One of the dogs had normal sodium and potassium, one dog had hyponatremia and hyperkalaemia and in another one electrolyte concentrations are unknown.

Friedenberg et al[28] characterised the lymphocytes within the adrenal glands in three dogs with "typical" and two dogs with "atypical" hypoadrenocorticism as being primarily CD4+. In one of the latter two dogs the intensity of the inflammation within the adrenal cortex was milder than in the other dogs, the different zones, however, were not specified.

Buckley et al[29] described a 2-year-old German Shephard with "atypical" hypoadrenocorticism which was euthanised due to progressive weakness and neurological deficits. Post-mortem examination revealed intravascular lymphoma. In both adrenal glands the architecture of the zona fasciculata and zona reticularis was disrupted by blood vessels congested with neoplastic T-lymphocytes, whereas the zona glomerulosa was normal.

Unfortunately, aldosterone had not been determined in any of those cases. It therefore remains unknown, if those with (partially spared) zona glomerulosa or mild inflammation had normal secretory function.

Aldosterone concentrations in dogs with 'typical' and 'atypical' hypoadrenocorticism

Evaluation of aldosterone is not routinely included in the work-up of dogs with suspected hypoadrenocorticism. In dogs with confirmed "typical" hypoadrenocorticism it seems logical that not only the cortisol, but also the aldosterone, secretory capacity is affected. Until recently aldosterone concentrations had only been measured sporadically and it was therefore unknown if there are differences in aldosterone concentrations between dogs with mild, and dogs with severe, electrolyte abnormalities. We investigated aldosterone concentrations in 70 dogs with primary hypoadrenocorticism, in 22 dogs with diseases mimicking hypoadrenocorticism and in 19 healthy control dogs[3]. Sodium and potassium concentrations in the 70 dogs with hypoadrenocorticism ranged from normal (four dogs) to severely abnormal. Baseline and post-ACTH aldosterone concentrations were significantly lower in dogs with hypoadrenocorticism than in the other two groups of dogs. In 64/70 dogs with hypoadrenocorticism baseline and post-ACTH aldosterone concentrations were below the detection limit of the assay (RIA). In 6/70 dogs post-ACTH aldosterone was below or in the lower half of the reference interval, all six dogs had hyponatremia and 3/6 had additional hyperkalaemia. Interestingly, in all four dogs with "atypical" hypoadrenocorticism baseline and post-ACTH aldosterone concentrations were below the detection limit of the assay. After the study was published we measured baseline

and post-ACTH aldosterone in another four dogs with “atypical” hypoadrenocorticism and found it to be below the detection limit of the assay in three of them, one dog had low-normal baseline aldosterone with no increase after ACTH. The finding that aldosterone concentrations were low or undetectable in most dogs with hypoadrenocorticism independently of the degree of electrolyte abnormalities – and even in dogs with normal electrolytes – was striking. This means, that normal electrolytes do not necessarily reflect a normally functioning zona glomerulosa.

In human medicine, normal sodium and potassium concentrations are found in 10% and normal potassium in 25% of patients with primary hypoadrenocorticism[30]. The assumption that the zona glomerulosa and the aldosterone secretion are still intact in these patients has been degraded. Increased renin concentrations were found in all of those patients, indicating compensation for a failing zona glomerulosa. Therefore in humans, it is currently assumed that a dissociation between zona glomerulosa and fasciculata/reticularis function occurs very rarely[31]. Possible mechanisms allowing a normal potassium balance without aldosterone are a high tubular flow rate with high delivery of potassium to the collecting duct and/or an increased sensitivity of the tubule to aldosterone due to up-regulation of the receptor. Furthermore, hyperkalaemia itself increases potassium excretion. It is also thought that normal potassium balance can be maintained as long as sodium intake is sufficient to maintain normal extracellular volume and distal tubular flow rate.[32,33]

Aldosterone was measured in dogs with “atypical” hypoadrenocorticism in a few other studies. Dunn and Herrtage found normal basal aldosterone but not increase after ACTH in one dog[34]; Thompson et al reported normal post-ACTH concentration in one dog[15]; Cartwright et al found normal baseline and post-ACTH aldosterone in a dog with Schmidt syndrome[35], however, both concentrations were in the lower end of the reference interval.

Treatment and follow-up examinations

In Zurich dogs with “atypical” hypoadrenocorticism are treated with prednisolone only, i.e. they do not receive mineralocorticoids. Initial dose is 0.5 mg/kg SID or BID (+ IV infusion if necessary), which is tapered to the lowest possible dose within 2-3 weeks after recovery. Most dogs receive 0.05-0.1 mg/kg SID prednisolone long-term. In the majority of dogs electrolytes remain normal. In the largest study so far electrolyte abnormalities developed in 5/35 (14%) dogs with “atypical” hypoadrenocorticism[8]. This finding is in agreement with a 9% and 11% conversion rate of other studies and our own data.[4,12,15] Conversion usually occurs during the first months of therapy, but has also been reported after four years. The risk of conversion requires good client communication and regular re-evaluations.

Redefining ‘atypical’ Addison’s disease?

The topic of “atypical” hypoadrenocorticism is quite complex and the question about the correct definition is challenging. According to currently available data dogs with “atypical” hypoadrenocorticism do not represent a homogenous group and at least three subgroups may be identified. Most dogs with primary hypoadrenocorticism and normal sodium and potassium concentrations have undetectable or very low aldosterone levels. It is very likely, that in those cases not only the zona fasciculata/reticularis but also the zona glomerulosa is destroyed.

The reason why the dogs are able to maintain normal electrolyte concentrations is currently unknown. A few dogs with primary hypoadrenocorticism and normal electrolytes have normal (usually low normal) aldosterone concentrations with no or very little increase after ACTH. It is possible, that in those dogs the zona glomerulosa is only partially destroyed at that particular point in time. As described above, segmental sparing of the zona glomerulosa has been reported. It may be that with time the destructive, immune-mediated process will finally involve all three zones equally, although this assumption is nearly impossible to prove. Successive loss of the different zones of the adrenal gland is certainly a rare event. Interestingly, one case report documented a dog with initial hypoaldosteronism, followed by hypocortisolaemia six weeks later[36]. In a third – most likely very small – subgroup of dogs with primary hypoadrenocorticism and normal electrolytes the immune-mediated destruction only involves the zona fasciculata/reticularis and the zona glomerulosa is normal. It is likely, but currently unknown, that those dogs have normal aldosterone concentrations. In principle only those dogs would 'deserve' the term "atypical" hypoadrenocorticism.

Concluding remarks

During the work-up of dogs with suspected hypoadrenocorticism and normal sodium and potassium several measures are important to consider:

- Most important is to exclude previous steroid application.
- An EDTA sample for measurement of endogenous ACTH should be taken prior to the administration of synthetic ACTH, centrifuged immediately and stored at -20°C.
- If the ACTH stimulation test confirms hypoadrenocorticism endogenous ACTH should be measured to differentiate between primary and secondary hypoadrenocorticism.
- Increased ACTH confirms primary hypoadrenocorticism, low ACTH is suspicious for secondary hypoadrenocorticism. In the latter case, imaging of the pituitary gland should be considered.
- In case of primary hypoadrenocorticism, measurement of aldosterone additional to measurement of cortisol (in the pre- and post-ACTH samples) would be interesting, however, will not have implications for treatment. It will be low in most of the cases.
- Glucocorticoid treatment should be initiated and tapered to the lowest possible dose.
- Regular re-evaluations (initially every 2-3 weeks) should be performed, to ensure that electrolytes are still normal.

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Management of an acute Addisonian crisis

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Hypoadrenocorticism is characterised by a deficiency of glucocorticoid +/- mineralocorticoid production and is usually caused by primary adrenal gland dysfunction. Although a potentially life threatening endocrine emergency, if diagnosed promptly and treated appropriately the majority of acute Addisonian crises represent rewarding cases to treat.

An index of suspicion for an Addisonian crisis is usually prompted by a combination of historical signs, physical exam findings and clinicopathological abnormalities. These clinical signs can vary widely on a case to case basis but often reflect the deficiencies of each hormone: glucocorticoid deficiency is typically associated with signs referable to the gastrointestinal tract (e.g. anorexia, vomiting, diarrhoea, melena) and clinicopathological changes such as lymphocytosis, hypocholesterolaemia and hypoglycaemia. Mineralocorticoid deficiency can cause hyponatraemia and hyperkalaemia, which in turn can precipitate hypovolaemia, bradycardia and collapse.

In general the following features may prioritise an Addisonian crisis amongst other differentials for collapse:

- Bradycardia or 'normal' heart rate despite findings of clinical dehydration.
- More severe dehydration than would be expected from the fluid losses (usually gastrointestinal) reported.
- Poor body condition despite only a recent history of disease.

Confirming the Diagnosis

It is not appropriate for hypoadrenocorticism to be diagnosed on compatible clinical signs and electrolyte changes alone and confirmation of a diagnosis with an ACTH stimulation test is preferred prior to instigating treatment with corticosteroids. Unfortunately once steroid therapy has been initiated, it can be very difficult to obtain a diagnosis of hypoadrenocorticism due to cross reactivity of several steroid formulations with cortisol assays and the suppressive effect of many steroids on the hypothalamic-pituitary-adrenal axis. Steroid therapy is usually not required immediately for the emergency treatment of any collapsed patient, and therefore an ACTH stimulation test can always be performed before starting steroid therapy. Patients that genuinely have hypoadrenocorticism can be stabilised in the short term with fluid therapy and management of electrolyte levels. Steroid therapy should be withheld until pre- and post-ACTH serum blood samples have been obtained.

Although measurement of basal cortisol concentration is perceived as a useful “rule out” test, it should not be used in patients where an acute Addisonian crisis is suspected. Instead, in these patients a full ACTH stimulation test should be performed in an attempt to obtain results faster, instigate therapeutics sooner and hopefully minimise cost to clients.

Goals of Treatment

In the event of an acute adrenal crisis, the main goals of emergency management are to restore fluid volume, correct electrolyte abnormalities and to provide a rapidly acting source of glucocorticoid support. Long term mineralocorticoid support (e.g. DOCP, fludrocortisone) is not indicated at this point, and may even be harmful, until these objectives have been met.

Fluid Therapy

The clinical status and degree of dehydration of the patient will dictate both the rate and volume of fluids administered. A ‘goal-directed’ approach to fluid resuscitation is advised (dictated by pulse pressure, blood pressure, CRT, mucus membrane colour, mentation, heart rate etc.) but it is possible that shock rates of crystalloids (~80 ml/kg/hr) may be required for the first 1-2 hours. Usually 0.9% sodium chloride is the fluid of choice as most affected dogs are hyponatraemic however balanced potassium containing fluids (e.g. Hartmann’s) are not necessarily contraindicated; the dilutional effects of fluid therapy will still outweigh the small additive effect of potassium. Care however, should be taken in severely hyponatraemic patients (e.g. with a sodium concentration less than 125 mmol/l).

Hypoglycaemia

In patients presenting with concurrent hypoglycaemia then fluids should also be supplemented with dextrose. In patients with clinical signs of neuroglycopenia then a bolus of dextrose is required (0.5-1.0 ml/kg IV of dextrose 50% diluted at least 1:1) before a CRI of dextrose is commenced. Usually normoglycaemia can be maintained with a CRI of 2.5-5%. Dextrose concentrations >5% are rarely necessary but would have to be given through a central line (as peripherally would increase risk of thrombophlebitis).

Glucocorticoid Replacement

The glucocorticoids that are the most commonly cited in the management of acute Addisonian crises are dexamethasone, prednisolone and hydrocortisone. The latter has the advantage of also providing short acting mineralocorticoid support and is therefore likely to provide rapid correction of hyperkalaemia. Additionally hydrocortisone is relatively cheap with a long shelf life justifying its place on the pharmacy shelf. Previous studies suggest an infusion of hydrocortisone sodium succinate at a dose rate of 0.5 mg/kg/hour is likely to confer sufficient glucocorticoid and mineralocorticoid support for the treatment adrenal insufficiency.[1,2] The use of a hydrocortisone CRI in the management of acute Addisonian crises has been shown to be associated with a rapid clinical response and overall shorter durations of hospitalisation. It should, however, be emphasised that close monitoring of electrolytes is necessary, especially

in severely hyponatraemic patients as excessively rapid correction of sodium concentrations may occur[3].

Dexamethasone by contrast lacks mineralocorticoid activity but will provide a source of rapidly absorbable glucocorticoid. There is a wide range of doses currently reported in the literature ranging from near-physiological doses of ~0.05 mg/kg up to significantly higher doses of 4 mg/kg.[4,5] There is no evidence to suggest that extremely high doses of dexamethasone are warranted and indeed it is possible that such doses could contribute to gastrointestinal haemorrhage[6]. If treating with dexamethasone the author recommends a conservative bolus dose of 0.1-0.2 mg/kg/day IV dexamethasone (as dexamethasone disodium phosphate).

Ancillary Management of Hyperkalaemia

Ancillary management of hyperkalaemia in cases of hypoadrenocorticism is rarely necessary (especially where hydrocortisone is being used). However for dogs presenting with associated cardiac complications (i.e. severe bradycardia of less than 40 bpm) then 10% calcium gluconate may be necessary (0.5-1.5 ml/kg given as a slow intravenous infusion). While this will not lower serum potassium concentrations, it has the potential to reduce the excitability of cardiomyocytes. Neutral insulin and dextrose is commonly described in the management of hyperkalaemia (insulin encourages movement of potassium into cells thus lowering the extracellular potassium concentration). However while this approach is often successfully employed to manage hyperkalaemic complications of urinary obstruction/uroabdomen; caution is advised when considering this approach in dogs with hypoadrenocorticism (where hypoglycaemic complications are more likely to be encountered).

Patient Monitoring

The intensity of monitoring afforded to the patient is likely to be dictated by both the degree of patient compromise and, at least in part, by practice facilities and owner finances. Physiological parameters such as temperature, pulse rate and quality, respiration rate and non-invasive blood pressure measurement should be monitored at least hourly in severely compromised patients. Ideally electrolytes should be rechecked every 2-6 hours (as dictated by the severity of the patient's hyperkalaemia/hyponatraemia). Continuous ECG monitoring is advisable, however it should be noted that ECG abnormalities do not accurately correlate with serum potassium concentrations (and should consequently not be used in lieu of direct electrolyte measurement).

Overcorrection of Hyponatraemia

While the focus in managing patients in acute adrenal crisis is often directed at resolving hyperkalaemia, it is also imperative to monitor trends in sodium concentration. In patients with severe hyponatraemia (e.g. <125 mmol/l), too rapid a correction of sodium can lead to severe neurological complications. Chronic hyponatraemia is associated with adaptive responses that allow the brain to cope with hypotonicity, for example, within 1-2 days there is usually a decrease in cellular organic solutes (e.g. amino acids and polyols). It is this 'coping' response that predisposes the brain to injury when hyponatraemia is corrected too quickly. All the solutes purposefully lost during hypotonicity have to be recovered; a process that can take several

days. If correction of hyponatraemia occurs quicker than recovery of solutes then osmotic demyelination of the neuronal cells can occur. This is known as osmotic demyelination syndrome (or central pontine myelinolysis) and can be associated with dramatic neurological signs such as ataxia, postural deficits, dysphagia and decreased mentation.

It should be noted that these signs often lag by a couple of days behind the initial acute presentation and treatment event. Guidelines extrapolated from human medicine suggest sodium concentration should not increase by more than 12 mmol/l/day (or >0.5 mmol/l/hour). In order to prevent such complications, in patients presenting with severe hyponatraemia, treatment with 0.9% sodium chloride may not be appropriate and consideration should be given to low sodium-containing fluids (e.g. 0.45% sodium chloride). Similarly if hydrocortisone is being used a dose reduction may be appropriate.

Conclusions

Acute Addisonian crises, when managed with appropriate fluid therapy and glucocorticoids, are likely to be associated with a favourable outcome. Regardless of the choice of glucocorticoid support careful monitoring of sodium concentration is required to prevent osmotic demyelination.

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Treatment of Addison's disease with Zycortal and glucocorticoids

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Introduction

Once a dog with hypoadrenocorticism has been diagnosed and any acute signs stabilised then the chronic management can begin. At this time, it is important to discuss the chronic management of hypoadrenocorticism with owners. The lifelong nature of this treatment and the importance of not missing doses must be emphasised. It is also important to make sure that the clients understand that it may take several monitoring visits to find the right doses of glucocorticoid and mineralocorticoid. The clinical targets for these cases should be ambitious – properly treated dogs should have a normal body weight, appetite, thirst and demeanour without signs of glucocorticoid excess. Medications should be adjusted to achieve this and nothing less than this should be accepted. It is also desirable that treated dogs have normal concentrations of electrolytes but the consequences of mild abnormalities are not known.

An authorised long acting formulation of desoxycortone pivalate (DOCP) (Zycortal; Dechra Veterinary Products Ltd.) was released on to the European market in 2016. The active component of this preparation has been available in a similar form for several years in the USA.[1,2] It has been widely used and is generally regarded as a safe and effective treatment: even at 15-fold overdoses, side effects appear to be mild.[3,4,5] Guidelines are available for transferring dogs from fludrocortisone[6].

Glucocorticoid supplementation

All dogs must receive daily glucocorticoid treatment titrated to effect based on clinical signs. The author's starting dose of prednisolone is 0.1-0.2 mg/kg q24h for newly diagnosed cases. However, there are wide inter-subject variations in plasma concentrations after administration of prednisolone, which suggest variable drug absorption. Furthermore, no relationship has been demonstrated between these plasma concentrations (unbound or total concentration) and clinical response. It is therefore not surprising that the final dose varies considerably between individual animals and whilst a good proportion of dogs will ultimately be stable at 0.05-0.1 mg/kg q24h, some may be even lower. For dogs requiring particularly small doses of glucocorticoid, cortisone acetate could be considered as an alternative. Overdosing with glucocorticoids is common and it is important to ask owners if their dogs are showing any signs of polyuria/polydipsia, poor hair regrowth or increased bodyweight. In particular, poor hair regrowth at sites of venepuncture, in the absence of polyuria/polydipsia, can be seen in long term mild overdosing and owners may not notice this unless asked. Glucocorticoid deficiency causes lethargy (which can be severe), inappetence, weakness and gastrointestinal signs. Glucocorticoid dose adjustments should be made no more frequently than twice monthly and

dose increments should be +/-25 to 50% of the previous dose. At times of metabolic stress or illness, the glucocorticoid dose may need to be increased (2- to 4-fold).

It may be possible to use endogenous ACTH to assess glucocorticoid supplementation but more work is required before this can be suggested for routine monitoring.[7]

Mineralocorticoid supplementation

The authorised initial dose of DOCP is 2.2 mg/kg SC given approximately every 25 days[8]. Many authorities however use a starting dose of 1.5 mg/kg SC given every 28 days. It is very important to make sure that the product is properly resuspended before drawing up the injection (and the syringe should continue to be gently rotated after drawing up the dose before injection to avoid precipitation in the needle). Longer intervals (e.g. 35 days) increase the risk of instability (but may be cheaper for the client). There is no evidence that there is an extended duration of action but many dogs, if their dose is delayed, do not show electrolyte abnormalities for some time[9]. This is consistent with the long period between the onset of clinical signs and the development of electrolyte abnormalities seen before diagnosis in many cases.

Most dogs require adjustments to their initial dose and it is more likely that dogs will require a dose reduction than a dose increase if using a starting dose of 2.2 mg/kg. The decision to change the dose is made by assessing electrolytes and clinical signs. The aim is to keep potassium and sodium within their reference intervals throughout the dosing interval. To assess this, it is necessary to check at 10 (+/-3) and 28 (+/-3) days post injection after every dose until stable. Monitoring electrolytes at 10 days post injection enables assessment of the peak effect of the dose whereas the 28 day sample enables assessment of the duration of the dose. If the peak effect is too great (or too little) at 10 days post injection then the subsequent dose should be reduced (or increased). If the potassium is below and/or sodium is above their respective reference range at 28 days then DOCP should not be administered and electrolytes should be checked every 7 days until they are within their respective reference ranges and then DOCP administered (at a reduced dose of about 20% less than the previous dose). If the dog still has electrolyte abnormalities consistent with hypoadrenocorticism at 28 days, then DOCP must be injected at a higher dose (or the interval shortened).

A dog can be regarded as being on the correct dose of DOCP when it is clinically well and has electrolytes within their respective reference ranges on days 10 and 28 post injection for at least two consecutive treatment cycles using that same dose. Once the correct dose has been determined, dogs should be reassessed every 4-6 months at the time of (or just before) injection.

It is possible to lower monthly DOCP doses in some dogs (in some cases to much lower levels than the starting dose[10]). Such approach might be justified on cost grounds in some cases but this approach also requires more monitoring tests. It should also be noted that the study had a surprisingly high death rate (25%) though the authors suggest that the cause of death was never hypoadrenocorticism.

It is important to be aware that there are day to day variations in sodium and potassium concentrations (Unpublished results). There are also differences between results from different laboratory analysers that cannot be explained by different reference ranges[11]. Therefore, very small or inconsistent changes may not be clinically significant. If in doubt it is entirely appropriate

to repeat the measurement and/or give the same dose as previously. Frequent monitoring of electrolytes is not necessary and risks over-interpretation and excessive dose adjustments. Average stability is likely to be safer (and certainly cheaper) than constant re-titration.

Few side effects have been seen with DOCP but one that should be noted is that dogs may show polyuria/polydipsia from days 7 to 10 post injection. This is usually associated with a mild overdose of DOCP and a dose reduction at the next injection usually resolves this problem. It is important to distinguish this short-term side effect from the long-term polyuria/polydipsia seen with excessive doses of glucocorticoids.

One other side effect that has been noted recently is that some dogs treated with DOCP can develop higher blood pressures compared to when they are treated with fludrocortisone (unpublished observations based on 30 dogs). This is in contrast to previous studies with small numbers of patients which did not detect such increases[12]. This may be worth investigating in dogs whose owners report that they are unwell in the days following dosing, in case the cause is mild hypertension. The effect of chronic low grade hypertension is not known and cardiac performance of such patients is being assessed.

Owners should be encouraged to keep their own records of doses administered (support materials are available from Dechra Veterinary Products Ltd. and the author encourages their use). It is also important that owners are taught to give the injections themselves. Owners should be reminded regularly that should a dog become ill then additional glucocorticoids are rarely wrong, but veterinary advice should be sought as soon as possible.

Many European practitioners are becoming very familiar with DOCP however our experience is still limited and it is important that experiences are shared and discussed with relevant specialists and the company who supply the product.

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Zycortal Symposium Highlights

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What starting dose of Zycortal are we using?

Zycortal (DOCP) is licensed to be used in the treatment of dogs with primary hypoadrenocorticism, with concurrent glucocorticoid therapy, at a dose of 2.2 mg/kg subcutaneously every 25 days. The starting dose and dosing frequency were discussed and it was clear that most delegates are using a much lower starting dose, ranging from 1.5 to 2.0 mg/kg. Most delegates were using a dosing interval of every 28 days. Although this is a deviation from the data sheet, it was agreed that a four weekly dosing frequency improved owner compliance, allowing more consistent treatment of patients. It was advised that when reducing mineralocorticoid supplementation, the dose should be reduced, instead of increasing the dosing frequently the injections.

The starting dose of Zycortal in cats was also discussed, with the full 2.2 mg/kg dose being recommended every 28 days.

Measuring cortisol and confirming the diagnosis of Addison's disease

The measurement of cortisol was discussed and the use of in-house snap tests was discouraged. It was also recommended that a lab recognised by the European Society of Veterinary Endocrinology (ESVE) Quality Assurance Scheme be used .

Before performing an ACTH stimulation test, it should be ensured that there is no previous history of steroid administration. This includes topical eye and ear ointments and hormone therapies. There was variability in when ACTH stimulation tests are performed in patients with a history of prior steroid therapy. This was partly dependent on how recently steroid administration had been received and also the dose and length of therapy. It is also important to note that there is extreme variability in how the hypothalamic-pituitary-adrenal (HPA) axis is suppressed in patients who have received steroid therapy. In patients who were no longer on steroid therapy, it was recommended that the ACTH stimulation test be performed and repeated at weekly intervals until stimulation was documented, or the clinician was confident that the patient had Addison's disease. If finances were limited then two to three weekly intervals could be used instead.

If patients were on oral prednisolone therapy at the time when an ACTH stimulation test was to be performed, then if possible, it would be advisable to drop to a physiological dose of

prednisolone (around 0.08 mg/kg daily) and perform the test one week later. If a flat lined response was obtained, then repeating of the stimulation test would be recommended one to two weeks later. The cross-reactivity of some exogenous steroid preparations with the cortisol assay (prednisolone and hydrocortisone) is as equally important to consider as the suppression of the HPA axis.

It was clear that basal cortisol (>55nmol/l) was frequently being used as a rule out test for hypoadrenocorticism, in patients with non-specific chronic signs. In patients with a high index of suspicion for the disease, it is still recommended to proceed with an ACTH stimulation test, however for financial and practical reasons, basal cortisol should be considered in patients with signs such as chronic gastrointestinal signs. It was discussed whether or not basal cortisol should be included in routine biochemical panels as this may increase the diagnosis of atypical cases of Addison's disease in practice. However it was decided that this may lead to incorrect diagnosis of the condition or lead to an increased number of ACTH stimulation tests being performed in patients unlikely to have to condition. Instead, it was decided that first opinion vets should be educated on the use of basal cortisol in patients with chronic gastrointestinal signs or chronic weight loss.

What is "atypical" Addison's disease?

This has been a controversial and extensively discussed subject in the past. It was recognised that there may be three subgroups of "atypical" Addison's disease:

1. Normal electrolytes, low aldosterone. In these patients there would appear to be destruction of the zona glomerulosa as well as the fasciculata/reticularis. The electrolytes would appear to be normal due to compensatory mechanisms.

2. Normal electrolytes, normal aldosterone, no stimulation of aldosterone following ACTH stimulation. In these patients, it is speculated that only partial destruction of the zona glomerulosa exists. Ongoing destruction of the zona glomerulosa is possible and therefore the aldosterone could subsequently become low.

3. Normal electrolytes, normal aldosterone, stimulation of aldosterone following ACTH. This group represents the true "atypical" group, who appear to have destruction of the zona fasciculata/ reticularis only.

It was agreed that the term "atypical" Addison's disease should be used for the third group. The first group should be termed "typical primary hypoadrenocorticism with normal electrolytes" and group two "typical primary hypoadrenocorticism with normal electrolytes and partial aldosterone deficiency".

How are glucocorticoids being supplemented when using Zycortal (DOCP) for mineralocorticoid supplementation?

Prednisolone appeared to be the most commonly used drug for glucocorticoid supplementation. Cortisone was mentioned as an alternative, as it allowed smaller doses to be given accurately. However this drug is expensive and requires an import license, meaning it is rarely used. An alternative for patients requiring a particularly small dose is a paediatric preparation (prednisolone 10 mg/ml; Focus Pharmaceuticals Ltd.) of prednisolone which is available in a liquid form. This drug can be used under the cascade when tablet sizes of prednisolone become limiting.

The most commonly used starting dose of prednisolone was 0.2 mg/kg, however dose increases seem to be very rarely required long term and most patients seem to require a dose reduction. It was discussed that the dose of prednisolone is extremely variable, even within breeds. Therefore it is important to consider each patient individually when adjusting prednisolone doses. It was noted that dogs diagnosed at a young age require higher doses of prednisolone, which are then later reduced.

The need for an increased dose of prednisolone was also discussed at length and opinions on this subject were extremely variable. It was agreed that the glucocorticoid requirements were increased during times of metabolic stress. However there was a difference in opinion regarding when a dose increase should be considered. Some specialists recommended a dose increase at any time of potential emotional or metabolic stress, including: kennelling, a trip to the vets, firework season, concurrent illness or surgery. Alternatively, other specialists recommended a dose increase only for metabolic stress such as illness or elective surgery. It was recommended that should a patient seem lethargic or dull following a trip to the practice, it should pre-emptively have a dose increase of prednisolone prior to any subsequent consultations.

There was also variability in the amount that the prednisolone dose was increased by. It was noted that in human medicine, the dose can be increased by up to twenty times. In canine patients the dose generally seemed to be increased by two to five times. The dose increase used is subjective, with extremely sick patients having a more marked dose increase compared to patients who are anticipated to experience emotional stress.

Monitoring and treatment of Addisonian patients with normal electrolytes

The monitoring and treatment of patients with normal electrolytes is largely dependent on the aldosterone levels. If truly an atypical case (i.e. normal aldosterone) then only glucocorticoid supplementation is required. It is however recommended that the aldosterone (or at least the electrolyte) levels are monitored as there have been atypical cases reported who subsequently develop aldosterone deficiency. Aldosterone/electrolyte levels should be monitored every 3-6 months, or sooner should the patient seem unwell in any way.

As for patients with normal electrolytes and abnormal aldosterone, the majority of specialists agreed that mineralocorticoid supplementation should be administered; as relying on compensatory mechanisms when there is a deficiency in aldosterone increases the chance of the patient presenting in an Addisonian crisis. The starting dose of DOCP used in these cases should however be reduced to around 50% of the licensed starting dose. Other specialists advised that if finances allowed frequent electrolyte monitoring, then they would wait and start DOCP at a routine dose once electrolyte abnormalities have been documented.

Should elective surgery be considered in dogs with Addison's disease?

In stable Addisonian patients, there is no need to avoid elective surgery if it will benefit the patient. The prednisolone dose should however be increased to two to three times the standard dose. A temporary increase in prednisolone dosage for around 2 to 5 days post-surgery, should not affect wound healing. A constant rate infusion, or at least boluses, of hydrocortisone can also be considered to improve anaesthetic stability during anaesthesia and recovery from surgery.

There was discussion of entire female Addisonian patients who have not stabilised on treatment with DOCP and prednisolone. It is suspected that this could be due to sex hormones having cross reactivity with other steroid receptors. It was concluded that all entire female dogs should not necessarily be neutered, however neutering should be considered in entire dogs who are difficult to stabilise. It is also advised that pregnancy be avoided in these patients.

Interpretation of polyuria and polydipsia in patients being treated with prednisolone and DOCP for management of hypoadrenocorticism

Difficulty has been encountered when stabilising patients on DOCP and prednisolone due to the signs of polyuria and polydipsia (PU/PD). As these signs are commonly encountered with prednisolone therapy, this can lead to excessive reduction in the prednisolone dose. However it is important to note that DOCP can also cause PU/PD, most likely due to transient hypokalaemia. It is important therefore to consider the timing and onset of these signs. Prednisolone therapy causes constant PU/PD, whereas DOCP causes PU/PD more notably at around day 10 following injection. Therefore a dose reduction in DOCP should be considered, rather than a reduction in the prednisolone dose.

Conclusion

Although experience is yet to be gained in using Zycortal, it was agreed by all delegates and specialists at the Symposium that the introduction of Zycortal to the European market has greatly improved the quality of the management of patients with typical hypoadrenocorticism. It was agreed that this preparation of DOCP was not interchangeable with Percorten-V®, a licensed preparation of DOCP used in North America. Zycortal so far has seemed a much more potent drug and it is therefore important to continue to strive to improve our use of this drug by continuing studies, instead of extrapolating information from previously published reports. This meeting of key opinion leaders was an extremely useful exercise, allowing vets to compare experiences of managing Addisonian patients and hopefully leading to improved management of patients with hypoadrenocorticism.

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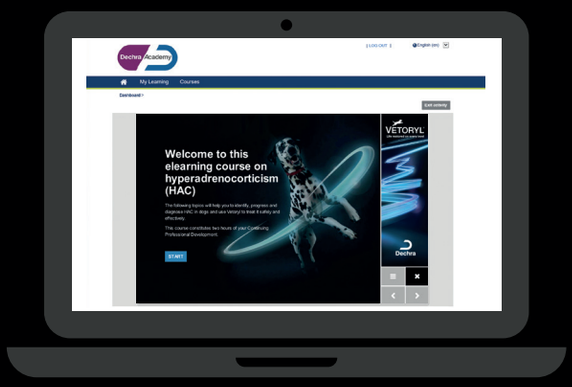

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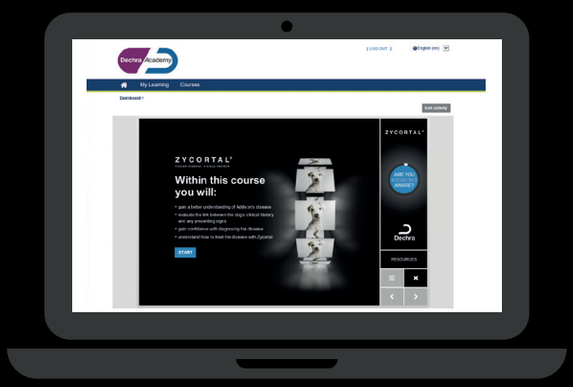

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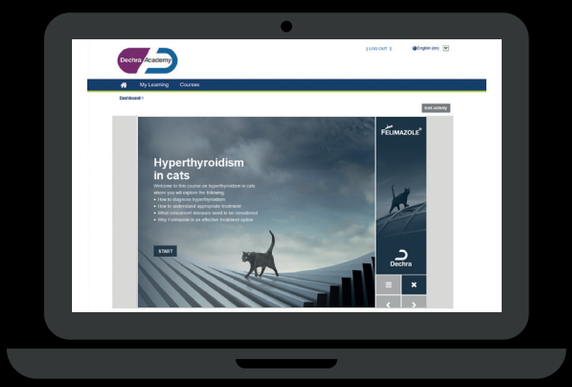

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