INTRODUCTION:

Although ultrasound is less sensitive than computed tomography in assessing the adrenal glands it is the preferred primary method of assessment due to its accessibility in veterinary practice.

The indications to ultrasound the adrenal glands are largely to support a presumptive diagnosis of hyperadrenocorticism and to further differentiate between adrenal-dependant and pituitary-dependant hyperadrenocorticism. Further indications include investigating peritoneal or dorsal abdominal masses, hypertension and other clinical signs which may be related to phaeochromocytoma and to search for metastasis.

NORMAL ULTRASONOGRAPHIC ASSESSMENT

Patients can either be positioned in dorsal or lateral recency. It is essential to use a high frequency transducer to visualise the adrenal glands and a thorough knowledge of the regional vasculature is required to locate the adrenal glands.  

With the patient in right lateral recency, the left adrenal gland can be visualised by positioning the transducer caudal to the last rib and ventral to the lumbar muscles at the level of the left kidney. Utilising this ultrasound window, the aorta should be seen running in a cranio-caudal direction and will be the closer of the two large vessels. The left renal artery can be seen exiting the aorta directed caudally where after it immediately deviates cranially to reach the renal hilus. The adrenal gland is located between the aorta and the left kidney, cranial to the hook made by the renal artery (Figure 2 B).  

With the patient positioned in left lateral recency, and with the transducer in a similar position as on the contralateral side, the caudal vena cava and right kidney are located as landmarks to visualise the right adrenal gland. The right adrenal gland abuts the caudal vena cava. The right adrenal gland is more challenging to find than the left gland. 

A similar approach is used when locating the adrenal glands in feline patients, however the glands are consistently more cranially located along the main abdominal vessels, lying just cranial to the cranial pole of each respective (left and right) kidney. 

The left adrenal gland is peanut shaped in smaller dogs and elongated and slender in medium to large breed dogs. (Figure 1 A and B) The right adrenal gland has been reported to have an “arrow” shape or L-shaped. The glands are typically uniformly hypoechoic however an outer hypoechoic rim and hyperechoic inner zone may be differentiated with progressive imaging techniques and equipment. This distinction represents the outer cortex and inner medulla. (Figure 1 C) 

Feline adrenal glands are typically more oval bilaterally and homogenously hypoechoic. It is rare to see the cortico-medullary distinction in a cat. Mineralisation of the adrenal glands is common in cats, occurring in up to 50% of the population. Such glands are hyperechoic with a distal acoustic shadow. This change does not however affect the size of the gland. Contrary, mineralisation in canine adrenal glands has a high probability of representing malignant change although rarely it may be due to dystrophic change. 

The cut-off for maximum adrenal gland size in the dog has been commonly referenced is 0.74mm for either the cranial or caudal pole in either a sagittal or transverse plane regardless of body weight of the patient. However a more recent study (n=45), it was found that the size of the adrenal gland in patients without clinical evidence of hyperadrenocorticism varied with three weight categories. The guidelines from this study are as follows:
Maximum thickness of the caudal pole of the adrenal gland in sagittal plane:

- Dogs ≤ 10 kg: ≤ 0.54 cm
- Dogs 10-30 kg: ≤ 0.68 cm
- Dogs ≥ 30 kg: ≤ 0.80 cm

However, the authors do acknowledge limitations to the study, such as the low study numbers and the need to further investigate at risk populations of dogs in order to fine-tune these cut-off values. It has been found that the caudal pole thickness of either adrenal gland in a sagittal plane was the best dimension for evaluating adrenal gland size due to low variability, ease and reliability in measurement.

Ultrasound is however, not a flawless technique and up to 25% of dogs with pituitary–dependant hyperadrenocorticism can have normal adrenal gland size on ultrasound and some healthy dogs will have adrenal glands larger than the recommended cut-off values. Therefore, the ultrasonographic findings should be interpreted in light of the clinical signs as well as the clinic-pathological test results.

In cats, the normal adrenal glands are 10-11 mm in cranio-caudal length and up to 4.3 ± 0.3 mm in diameter.

**PATHOLOGY OF THE ADRENAL GLANDS**

**Hyperplasia**

Patients with PDH generally have bilaterally symmetrically adrenomegaly with a plump rounded appearance. This is attributable to the cortical hyperplasia secondary to pituitary disease. However, in some patients with PDH there may be asymmetrical enlargement due to nodular hyperplasia and in these cases it may be difficult to distinguish the enlarged hyperplastic gland from an adrenocortical adenoma.

Another aetio-pathogenesis for bilateral adrenomegaly is Trilostane therapy. This is due to cortical hypertrophy secondary to reduced cortisol production and the diminished negative feedback mechanism. Following Trilostane treatment, the glands can also become heterogenous in nature or have an enhanced cortico-medullary distinction. It is therefore imperative to perform ultrasonographic assessment of the adrenal glands prior to initiating Trilostane treatment.

**Neoplasia**

Primary adrenal tumours are generally unilateral but bilateral tumours have been reported. In patients with clinical signs of hyperadrenocorticism and the finding of an adrenal gland nodule on ultrasound can prove a conundrum. This finding may be due to an adenoma, an adenocarcinoma or a hyperplastic nodule and none of these changes have specific ultrasonographic changes.

The following guidelines apply in such cases:

- Masses ≥ 2.0 cm and/or showing mineralisation are considered less likely to represent hyperplastic change with a benign or malignant lesion more likely.
- Masses ≥ 4.0 cm are more likely malignant than benign.

Besides a diagnoses of adrenocortical tumours, other tumours occurring in the adrenal glands include myelolipomas, phaeochromocytomas and metastatic tumours. Benign lesions such as cysts, granulomas and haematomas can also mimic neoplastic change in the adrenal glands.

Myelolipomas are benign, endocrinologically inactive tumours. Their fatty component results in them being hyperechoic on ultrasound.

Phaeochromocytomas are rare catecholamine secreting tumours. Patients present with vague clinical signs either due to the secretion of catecholamines or due to the space occupying lesion in the retroperitoneal space. These tumours are incredibly rare in feline patients.

Several tumours metastasise to the adrenal glands; mammary, prostatic, gastric and pancreatic carcinomas, squamous cell carcinomas, transitional cell carcinomas, malignant histiocytosis,
melanomas and haemangiosarcomas. Thus if a patient is suspected of having one of these tumours, a full metastasis search should be performed with careful interrogation of the adrenal glands.

**Vascular invasion**

Adrenalectomy is the treatment of choice for adrenal tumours. Regional vascular invasion or tumour thrombus is reported to be as high as 82% for phaeochromocytomas and between 11% to 41% for adrenocortical tumours. Vascular invasion has been reported to occur via the phrenicoabdominal vein with echogenic material reported in the phrenicoabdominal and renal veins and the caudal vena cava as a result of extension. Although vascular invasion is more common with tumours affecting the right adrenal gland, aggressive tumours of both glands can invade the caudal vena cava (Figure 3). Tumour thrombus has been associated with a shorter survival time. A negative finding for local vascular invasion on ultrasound is however not sufficient to exclude the possibility and it is advocated that if surgical treatment is intended, a computed tomography study is performed for optimal surgical planning.

**Adrenal gland atrophy**

If a patient is suspected of having hypoadrenocorticism, then a finding of small adrenal glands or the inability to find the adrenal glands supports this diagnosis. A cut-off value has been documented as ≤3.0mm thickness for the left adrenal gland and ≤3.4mm for the right adrenal gland. However, once again, ultrasound alone cannot be used to make a diagnosis of adrenal gland atrophy. Other causes for non-visualisation of the adrenal glands include incorrect transducer selection/ultrasound technique, poor image quality due to gas in the GIT or patient panting and exogenous steroid administration.

**CONCLUSION**

Ultrasound is the preferred first choice modality for adrenal gland assessment in patients with suspected pathology. However, there is a certain degree of overlap in the ultrasonographic appearance of healthy and diseased glands as well as non-specific pathological changes making a definitive diagnosis bases on ultrasonographic findings alone impossible.

It is therefore imperative to correlate ultrasonographic findings with clinical signs and any clinic-pathological test results in order to make a definitive diagnosis. In many cases of adrenal tumours, a definitive diagnosis will only be made at necropsy.

If a nodule or mass is found, following the necessary function tests, it advised to do follow up ultrasound studies every 3 – 6 months for monitoring purposes.

**References**

Treatment options for Pituitary Dependent Hyperadrenocorticism (PDH)

By Dr L L van der Merwe, BVSC (MMedVet(Med))

Surgical options written by Dr Marlies Bohm

PDH is the most common (82%) form of canine hyperadrenocorticism. Any treatment whether surgical or medical will require life-long medication and some hormone monitoring.

A. Surgical resection of the pituitary tumour (trans-sphenoidal hypophysectomy)

Surgery is the treatment of choice for humans. Bjorn Meij of Utrecht pioneered the surgery (trans-sphenoidal hypophysectomy) and has operated on > 200 dogs and cats. With surgery the cause of the problem is addressed whereas with medical management control is aimed at limiting the effects of the pituitary tumour

If your patient is starting to show neurological signs and the CT/MRI indicate that the tumour is still operable then surgery is really your best choice. If your patient is relatively young you could also consider surgery – because if he is expected to survive for many years assuming his Cushing’s is controlled then it means there are many years for the pituitary tumour to grow.

There are some pituitary tumours that are too large to be removed. The bigger the tumour the greater the risk associated with surgery and the lower the chance that the tumour can be completely removed.

Dr Meij is prepared to fly out from Utrecht and perform the surgery at Onderstepoort. The post op period is tricky and requires constant supervision in ICU. You will need to cover the costs of Dr Meij’s flights, his professional fee for the surgery and Onderstepoort’s fee. The last case cost the owners approx. R50 000. (Feb 2014). Contact Dr Marlies Bohm (marlies@wol.co.za) if you are considering this option - she organised this for a patient recently.

Prognosis:

92% of a group of 150 dogs survived surgery and the immediate post op period and the survival rates are expected to be even higher in new cases. In 9/150 (6%) dogs the surgeon wasn’t able to remove all the tumour.

• In 25% of dogs signs of Cushing’s recurred 6 weeks – 56 months (median 18 months) post operatively.
• 75% of patients stayed free of signs of Cushing’s and died of unrelated diseases. These dogs lived for an average of 28 months (range 2-87 months) after surgery. This doesn’t sound terribly long, but Cushing’s typically affects middle aged to elderly dogs that have a limited life expectancy in any case.

Post op treatment:

All dogs will need thyroid hormone supplements and hydrocortisone post operatively. The hydrocortisone dose is slowly weaned down to a fairly standard least effective dose.

• The thyroid hormone dose needs to be adjusted to the individual dog.
• The hydrocortisone dose is increased during times of stress (illness, travel, kennelling, hunting).
Dogs may need DDAVP (a synthetic form of antidiuretic hormone also known as vasopressin) transiently in the immediate post-operative period.
  - Based on 150 operated dogs: 47% of dogs can stop taking DDAVP within 2 weeks of surgery and an additional 31% could stop eventually. The remaining 22% needed it for life.

B. Treatment with mitotane (Lysodren = o’pDDD)

Mitotan, the first effective treatment for Cushing’s, destroys the cortisol producing cells in the adrenal gland. Lysodren is not licensed for use in SA and a section 21 application is required. (See Box)

<table>
<thead>
<tr>
<th>survival</th>
<th>1 year</th>
<th>2 year</th>
<th>3 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of surviving dogs with no recurrence of Cushings disease</td>
<td>77%</td>
<td>53%</td>
<td>44%</td>
</tr>
</tbody>
</table>

Induction:

**Lysodren dose - 50mg/kg oid**

- Start induction on a Thursday / Friday so that the chances of drama on a weekend are diminished as the process generally takes 5 – 10 days.
- The pills are given in the morning after breakfast has been eaten.
- If the dog fails to wolf down his breakfast as normal - then withhold the medication for that day and perform an ACTH stim test (on the same day if possible). Do not administer any further lysodren until you have your results.
- The target of induction is a post stim cortisol of 25 – 125nmol/L. Unless the dog is showing clinical signs of addisons disease - don’t panic - you have stopped the treatment and the drop will slow down. If the cortisol is <25nmol/L you may supplement with 1mg/kg prednisilone for a few days. I generally wait 1 week after this sample and then start the weekly maintenance regimen. If the cortisol was <25nmol/L you may want to repeat the ACTH stim to make sure it is in the target range before starting the maintenance therapy - this may take a few weeks in some cases.
- Once on maintenance therapy repeat ACTH stimulation test after 4-8 weeks to see where the maintenance dose is keeping the cortisol. The target once again is 25 – 125nmol/L. I personally find this a bit low - especially if sampled just prior to next dose (trough level) and am happier with a level between 50 – 150nmol/L.
- Note timing of sampling is important: peak effect (i.e. lowest cortisol) a day or so after dosing, lowest effect (i.e. highest cortisol) just before next dose. Make a note of this for proper comparison of cortisol levels

**Maintenance: Lysodren 50mg/kg, 1 – 2 x/week**

- If your patient is ill /otherwise stressed (e.g. kennelled, going hunting) you may need to supplement low doses of cortisol (prednisone) on those days.

Complications:
• **Approximately 25% of dogs show one or more adverse effects during loading and approximately 33% develop a sign of overdose at some time during maintenance treatment**
• **Overdosing**: despite all instructions and counselling, 6-10% of dogs receive excess mitotane and become transiently or permanently Addisonian at some stage in their treatment
• **Gastric irritation**: vomiting / diarrhoea may be caused by problems other than the treatment. Giving the drug with food reduces the likelihood this side effect.
• **Lack of response to treatment**: a few dogs have needed > 60 d of daily treatment before their cortisol production decreased. These may do better on trilostane.
• **Sudden expansion of a pituitary mass**: Sometimes the pituitary tumour can enlarge and start causing neurological deficits. In some dogs this happens during the induction phase.
• **Liver toxicity**: has been reported in some very rare cases.

**Response to treatment:**

• The pu/pd and polyphagia usually improves dramatically during the induction phase and normalises in most, not all cases.
• Weight loss will take some months obviously.
• It will take some months for the serum chemistry to normalise.
• The skin may take up to 6 month to recover. It may actually get worse for 1-2 months before starting to improve.

**Advantages:**

• This is the only **medical** treatment option if your dog has calcinosis cutis (calcium deposits in the skin) or myotonia (muscle stiffness).
• You only need to medicate 1-2 x a week
• It is more cost effective than trilostane

**C. Treatment with trilostane**

Trilostane inhibits conversion of pregnelone to progesterone, a precursor for cortisol and aldosterone – thus both hormone levels are decreased, aldosterone to a lesser degree though. It is licensed in the UK, Europe and USA as a drug called Vetoryl®, which is not available in SA. Several compounding pharmacies produce a trilostane capsules in a variety of sizes. Around 90% of dogs with pituitary dependent Cushing’s can be well controlled with this drug.

**Survival times**:

PDH - 662 – 900 days vs mitotane 708 – 720 days (helm)

**Pharmacokinetics**

It is important to understand some of the pharmacokinetics of this compound as it affects dosing amounts, frequency and interpretation of tests monitoring treatment efficacy.

• Trilostane has low water solubility and an inconsistent absorption which is affected by the formulation. If your patient isn’t responding to trilostane or needs very high doses it MAY be because the drug is not being absorbed properly from the compounded version. If this is the case you could switch to imported Vetoryl and do a section 21 application.
• Absorption increases if dosed with meals.
• The duration of effect varies considerably between patients. Peak plasma levels are reached after 1.5 - 2 hour and back to baseline at 10 – 18 hrs. The drugs is generally active for about 13 hrs.

• Results of the ACTH stimulation test used for monitoring response to therapy varies depending on time after dosing of the (post pill).

• The peak drug levels will result in peak effect and maximum cortisol decrease at about 2 hours post pilling.
  o Cortisol levels were higher when the ACTH stimulation test is performed 4 hours versus at 2 hours post pilling. A current standard is to collect samples 4-6 hours post pilling.

• Due to a loss of negative feedback during trilostane treatment there is an increase in ACTH secretion, which in turn leads to increase size of adrenal glands in treated dogs.

• Adverse effects are self-limiting mild GI signs and rarely Addisonian type signs, requiring drug withdrawal or / and treatment. The increased endogenous ACTH secretion, especially at the higher starting doses initially recommended, caused adrenal necrosis. This side effect is much reduced with the lower effective doses utilised these days.

Dosing recommendations:
Initially the recommendations were 2-5mg/kg/day. This resulted in side effects and currently lower doses are achieving good results without the side effects.

  o 1.5mg/kg *oid* or divided *bid* in *am* with food. In larger dogs (>20kg) give slightly less than 1 mg/kg.
  o An early 2-week check-up is to make sure the post stim cortisol is not dropping too low. No dosage increases are made at this time.
  o BID treatment has been shown to require a lower overall drug dose. Studies show improved survival in dogs treated *bid* vs those treated *oid*. Median survival of 900d for *bid* vs 662 d for *oid* treatment. Which makes sense if, at best, the drug is only in the system for 13 hrs.
  o In dogs where clinical signs are still present and suppression is in the target range on oid treatment, *bid* medication is required as the effect of the drug is too short. In dogs with concurrent diabetes mellitus - trilostane must be used *bid* from the beginning to reduce insulin resistance.
  o Repeat ACTH stimulation test at 4-6 weeks post initiation of treatment to evaluate the effect of the drug on cortisol secretion. Dosage adjustments can now be made if required. Once the target post ACTH stimulation cortisol range of 50 – 150nmol/L, collected at 4-6 hours post pilling, is reached, monitoring can be done every 4-6 months.
  o If the post stim cortisol value is suppressed to <50 nmol/L then the medication is stopped for a week and restarted without performing and ACTH stim test. If the dog was showing any signs of inappetance, tremors and lethargy concurrently with a low post stim cortisol value then an ACTH stim test is performed prior to re-initiating treatment and treatment is only started again once cortisol levels rise into the target range. For some reason - even though the drug is just an enzyme inhibitor and has a short half-life – its effects can be quite lasting in some animals.

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5. 
Hypertension and proteinuria in canine cushings syndrome

DR Anthony Zambelli

Edited: Dr Liesel vd Merwe

Hypertension and proteinuria are 2 complications of cushings disease that should be tested for an managed. Up to 85% of dogs may have hypertension and 44 – 46% may have proteinuria and these conditions may persist despite successful management of the cushings disease. Because both proteinuria and hypertension are major factors in the development and progression of chronic kidney disease these conditions need to be managed in addition to the cushings.

Angiotensin converting enzyme inhibitors (ACEi) re used to decrease intra-glomerular hypertension as well as reduce mesangial proliferation and glomerular remodelling. When managing proteinuria, note that ACE Inhibitors such as enalapril and benazepril have special warnings for use in patients, they can cause an (initially reversible) azotaemia. You should have a baseline urea and creatinine. Recheck levels 2 weeks after initiating treatment in any patient, even a non-proteinuric patient. Re-check biannually as well. An initial dosages of 0.5 mg/kg q24h (for benazepril) and 0.5 mg/kg q12h (for enalapril) are appropriate; the dosage of both drugs can be increased if required, by giving q12h for benazepril and up to 1.0 mg/kg q12h for enalapril. These drugs can also be used as second- or third-line agents for controlling hypertension.

Amlodipine (0.2 – 0.4 mg/kg q24-12h) is the best agent for primary control of systemic blood pressure (SBP) >160 mmHg; for 140-160 mmHg, rather use an ACE inhibitor or angiotensin receptor blocker (ARB).

Never start a patient on anti-hypertensive agents on the basis of a single measurement, measurements in a very stressed patients or for SBP <140 mmHg. Rather re-evaluate in 5 – 14 days (sooner, for more hypertensive patients).

For example, in an asymptomatic cat with an initial SBP of 220mmHg, I would recheck in 3 – 5 days, ensuring a calm environment. In a symptomatic patient (cat with retinal detachment, gallop rhythm and a proteinuria, with a SBP of 190/130 mmHg), immediate antihypertensive therapy and hospitalisation is more appropriate.

When amlodipine is used, recheck the patient every 5 – 14 days, depending on the severity of the hypertension, and the UPC every 14 – 30 days, to chart response to therapy. Your target should be a UPC <0.2 and SBP 120-140mmHg with diastolic blood pressure (DBP) of 70 – 90 mmHg, no lower. Diastolic hypotension is as damaging to organs as hypertension.
Diagnosis of hyperadrenocorticism

By Sandy May BVSc (Hons), MMed Vet (KLD), PhD

Hyperadrenocorticism (HAC) occurs as a result of hyperplasia or neoplasia (Adrenal dependent hyperadrenocorticism - ADH) of the zona fasiculata of the adrenal cortex resulting in overproduction of cortisol. Hyperplasia of the adrenal gland will also result from an adenoma of the pars distalis or pars intermedia of the pituitary gland (pituitary dependent hyperadrenocorticism - PHD). Serum cortisol have a negative feedback effect on the production of ACTH and CRH by the pituitary and the hypothalamus. ACTH also has a negative feedback effect on the adrenal gland. In dogs the secretion of ACTH is pulsatile with 6-12 peaks in a day.

Any breed can develop hyperadrenocorticism but in general middle aged to older small breed dogs develop PDH and older large breed dogs develop ADH. The most common clinical signs associated with hyperadrenocorticism include polydipsia and polyuria, polyphagia, pattern alopecia (bilaterally symmetrical affecting flanks, ventral abdomen, neck and perineum), muscle weakness, thinning of skin, abnormal fat distribution with pendulous abdomen and hypertension. Rarer signs include calcinosis cutis and neurological signs.

Typical clinicopathological abnormalities include an increase in alkaline phosphate activity in 85% of dogs. Synthesis of this enzyme is induced by cortisol in the dog. There may be mild hyperglycaemia and hypercholesterolaemia and hypertriglyceridaemia are usually present.

There may be a slightly elevated RCC, Hb and PCV/ Ht. Thrombocytosis may be present and the characteristic stress leukogram of mature neutrophilia, lymphopaenia and monocytosis is present. Urine SG is <1.015 and usually in the hyposthenuric range. Proteinuria is frequently present and urinary tract infection is frequently found. Note that clinical signs are more important in selecting cases as the clinicopathological changes are not as specific.

Specific diagnostic tests:

A. Urine cortisol: creatinine ratio  
B. ACTH stimulation test  
C. Dexamethasone suppression test  
D. Endogenous ACTH

**A. Urine cortisol: creatinine ratio**

The urine cortisol: creatinine ratio (UCCR) has high sensitivity for HAC but low specificity. The normal reference range is <10 (<10 x 10^-6 – convention is to express this as 10), which effectively rules out a diagnosis of HAC. Due to the effect of stress the test only becomes more reliable when the cut-off is set at >100 (90% probability of PDH). However, a high ratio does not confirm HAC and further discriminating tests need to be done. The test has a good negative predictive value.
The cortisol and creatinine concentrations are measured on the same urine sample and the ratio is calculated as follows:

\[
\text{Cort:Creat} = \frac{\text{urine cortisol concentration (nmol/l)}}{\text{urine creatinine concentration (µmol/l)}}
\]

B. **ACTH stimulation test.**

The method for the ACTH stimulation test in dogs is as follows:\(^1\)

- The test can be started at any time of day
- Collect a blood sample for the basal cortisol concentration
- Inject 250µg of synthetic ACTH i.v or i.m. (125ug synthacten IM is effective)
- Collect a second sample 60 min later.

**Interpretation:**

- The baseline cortisol concentration is irrelevant
- A post stimulation concentration of >600nmol/l is consistent with a diagnosis of a diagnosis of HAC in a dog with typical clinical signs and showing no evidence of other clinical disease.
- This test reliably identifies approximately 84% of dogs with PDH and 51% of dogs with ADH\(^2\)

**Advantages:**

- The biggest advantage of this test is in distinguishing between iatrogenic and spontaneous HAC \(^3\)
- Monitoring response to treatment
- It is quick to perform
- It provides baseline information for treatment

**Disadvantage**

- It does not distinguish between PDH and ADH
- It is not very sensitive in detecting HAC caused by adrenal neoplasia

C. **Dexamethasone suppression tests:**

**Low dose Dexamethasone suppression test (LDDST)**

The low dose dexamethasone suppression test is an alternative to the ACTH stimulation test for the diagnosis of HAC.

**Method:**

- Collect a blood sample for the basal cortisol concentration
- Inject 0.01 mg/kg dexamethasone iv
- Collect samples at 4- 6 and 8 hours post-dexamethasone.
Figure 1
Interpretation (Figure 1)
• A normal response is suppression to below 40 nmol/l
• A complete lack of response could be consistent with PDH or ADH
• In most (approximately 85%) of PDH cases, there will be suppression to below 40 nmol at 4-6 hours and “escape” at 8 hours with an increase in cortisol concentrations.

Advantages
− The sensitivity is higher than the ACTH stimulation test (90-95%), thus fewer cases will be missed.
  o It has an almost 100% sensitive with adrenal neoplasia and 90 -95% sensitivity for PDH

Disadvantages
• The specificity however is very low if measured in sick dogs (44-73%) - thus a = 50% chance of false positives in non-adrenal illness.
• The test takes a long time (8h)
• It does not distinguish between iatrogenic and spontaneous HAC

A disadvantage of both these tests is that false positives may occur in animals with other chronic diseases. These include renal and hepatic disease, diabetes mellitus, neoplasia and chronic inflammation. False positives can be reduced by selecting patients carefully. Typical clinical signs of HAC should be present in patients selected for these tests and concurrent disease should be ruled out by clinical examination, clinical pathology and imaging.

High Dose Dexamethasone Suppression Test
This is NOT a screening test. It is used for discriminating between pituitary-dependent and adrenal-dependent hyperadrenocorticism. It has become less frequently used since ultrasound has become commonplace in practices.

Method:1,3
• Collect a blood sample for the basal cortisol concentration
• Inject 0.1 mg/kg dexamethasone iv
• Collect samples at 6 and 8 hours post-dexamethasone.

Interpretation:

• No suppression is consistent with ADH. The neoplastic cells function autonomously and are not subject to feedback suppression.
• Suppression to below 40 nmol/l is consistent with PDH.

D. Endogenous ACTH

This is the preferred test for HAC in horses but has not been used extensively in dogs.

Method:

The sampling conditions are very specific.

• The blood should be taken into chilled EDTA-aprotinin tubes. These should immediately be placed on ice.
• The plasma should be separated immediately in a (preferably) refrigerated centrifuge.
• The plasma should be transferred into a PLASTIC tube and immediately frozen.
• The sample should be sent to the laboratory frozen.

Interpretation[3]

• Normal dogs have an ACTH concentration of 3-10 pmol/l
• Dogs with PDH have concentration > 6.2 pmol/l
• Dogs with ADH have undetectable concentrations.

Advantages

• Single blood sample
• Easy discrimination between ADH and PDH

Disadvantages

• Specific sampling conditions
• Overlap between normal dogs and those with PDH

In summary:

• The urine cortisol: creatinine ratio is a good screening test but it cannot be used as a diagnostic test. Has a good negative predictive value
• The ACTH stimulation test and LDDST are most frequently used to diagnose HAC, but patients must be carefully selected to avoid false positives.
• The LDDST is more sensitive if an adrenal tumour is suspected.
• The high dose dexamethasone test and endogenous ACTH can be used to distinguish PDH from ADH but are rarely used.
REFERENCES


DEALING WITH INCIDENTAL ADRENAL TUMOURS

Kettner, F (MMedVet, DipECVIM-CA), Tygerberg Animal Hospital – Bellville, Cape Town, medicine@tah.co.za, Tel (021) 919 1191

An adrenal “incidentaloma” is an adrenal mass, found as an incidental finding during ultrasound or CT examination of the abdomen, where adrenal pathology is not initially suspected. In humans, the incidence varies from <1% to 7%, increasing with the age of the population. In canine and feline veterinary patients, most incidentally discovered adrenal masses, in otherwise healthy patients, are non-functional benign tumours or non-neoplastic lesions. Most functional adrenal masses are either cortisol secreting tumours or pheochromocytomas. In veterinary medicine, there is no consensus on the best approach to an incidentaloma. Deciding upon an appropriate treatment plan requires classification of the incidentaloma as malignant or benign and functional or non-functional.

Normal adrenal gland anatomy and physiology

The adrenal gland consists of an outer cortex and an inner medulla. The latter is the site of catecholamine production. The cortex has 3 zones: from the outside to the inside these are the zona glomerulosa, the zona fasciculata and the zona reticularis. The zona glomerulosa is responsible for the production of mineralocorticoids (aldosterone). Glucocorticoids (cortisol) and androgens are synthesized in both the zona fasciculata and reticularis.

In human medicine, the causes for adrenal masses include:

(a) Functional masses (up to 15%): adenoma (aldosterone or cortisol); carcinoma (any adrenal hormone); pheochromocytoma; congenital adrenal hyperplasia; massive nodular adrenal disease; nodular variant of Cushing’s disease

(b) Non-functional masses: adenoma; myelolipoma; neuroblastoma; ganglioneuroma; haemangioma; carcinoma; metastasis; cyst; haemorrhage; granuloma; amyloidosis; infiltrative disease

Hormones that are released from functional masses include: cortisol or one of the precursors (Cushing’s disease); aldosterone (Conn’s syndrome); sex hormones and adrenalin (pheochromocytoma).

The canine patient may be completely asymptomatic, as would be expected in a non-functional, small benign adrenal adenoma. Patients with functional adrenal masses may present with signs of the underlying hormone excess. Animals with malignant tumours (functional or non-functional), may show non-specific signs such as decreased appetite, weight loss, lethargy and nausea. Should metastasis be present, clinical signs will further depend on the organ/s which have been affected.

Surgical removal of functional or malignant adrenal masses would be ideal. However, not every mass needs to be removed and surgery holds significant risks to the patient, either due to age related anaesthetic issues, co-existing morbidity or due to surgical complications. On the other hand, surgically removing a pre-metastatic adrenal malignancy may be lifesaving.

General guidelines for surgical removal include masses that are larger than 3cm, show signs of malignancy, are functional or show invasion of the surrounding blood vessels. It may not be easy however, to determine the malignancy of a mass without cytological or histological evaluation.
The larger the mass the greater the likelihood of it being malignant. Both CT scanning and abdominal ultrasound have been shown to be sensitive for the detection of invasion of blood vessels. Although ultrasound was sensitive for the detection of thrombi in the caudal vena cava, it was only 75% sensitive for detecting all forms of invasion. In one study, invasion of the surrounding blood vessel was shown to occur via the phrenico-abdominal vein as opposed to the erosion of blood vessel walls. Pheochromocytomas seem to have prediction for invasion of blood vessels. Between 36-70% of all adrenal masses (benign or malignant) are seen to invade the surrounding blood vessels.

In humans, CT scanning is an additional factor that is used to decide on adrenalectomy. Benign masses tend to have a Hounsfield unit of <10% and a >50% contrast washout. Inhomogeneous masses with an irregular border are less likely to be benign, especially if the HU is > 20. In those cases that warrant surgical removal, pre-operative investigations for metastasis should be done. A CT scan of the thorax and abdomen has a higher sensitivity for detecting metastatic lesions than thoracic radiographs and abdominal ultrasound. As discussed previously, in human medicine, the CT density of the adrenal mass has diagnostic significance.

Masses that are <3cm in size, those that are not producing hormones and those that show no invasion of the surrounding blood vessels may be left for careful observation. The size of the adrenal mass is reassessed at 1, 2, 4 and 6 months after initial diagnosis. Those masses increasing in size should be considered for adrenalectomy. The non-enlarging, stable mass should continue to be observed at 4-6 month intervals.

Pre-operative attempts to diagnose the etiological cause for the adrenal mass are essential. Surgical excision of an undiagnosed pheochromocytoma carries a significant risk for peri-anaesthetic / operative morbidity and mortality. These can be significantly lowered by medically managing this endocrine disorder pre-operatively. Functional adrenal testing is therefore essential prior to surgical removal – especially to detect the presence of a pheochromocytoma.

**Adrenal functional testing**

*Pheochromocytoma*: tachycardia and hypertension are the hallmarks of catecholamine release, but hormone release may be episodic. Patients may, therefore, be completely normal during the physical examination – and be normotensive. A wide variety of clinical signs may be noticed by the owner, including: collapse/weakness; panting, tachycardia/arrhythmias, restlessness, inappetence/anorexia, nonspecific lethargy, exercise intolerance, polyuria/polydipsia, and weakness. Testing for the presence of a pheochromocytoma in dogs has centred on the measurement of adrenalin metabolites in the urine, either absolute amounts per 24hrs or as measured by a ratio to creatinine. Ideally, a first morning urine sample is collected and a small amount of acid is added to the prevent degradation of the metabolites. Metanephrine and normetanephrine to creatinine ratios are readily available to veterinarians in South Africa through use of the human clinical pathology laboratories. Pheochromocytomas should always be considered malignant in dogs, with metastasis occurring in up to 40% of affected dogs.

*Hyperaldosteronism*: (Conn's syndrome). This condition is suspected in patients with hypokalaemia, hypernatremia and hypertension. All findings are not consistently present in all patients. So, while identifying these electrolyte disturbances in a patient with an adrenal mass is supportive for this diagnosis, the absence of these findings do not exclude a case of Conn’s syndrome. The condition is rare in dogs and cats. Low renin and high aldosterone serum concentrations are useful in diagnosing those suspected patients with unremarkable serum electrolyte concentrations. Aldosterone levels are easily tested for, renin requires special collection practices.
Hyperadrenocorticalism: (Cushing's disease) Both the ACTH stimulation test and low dose dexamethasone may be used to diagnose Cushing's disease. Most patients should have clinical signs consistent with Cushing's disease. In some cases it may be more appropriate to exclude hyperadrenocorticism as a differential. The urine cortisol to creatinine ratio is a highly sensitively test, but not very specific. Therefore it has a high negative predictive value. Patients with a negative result are unlikely to have Cushing’s; while a dog that tests positive may or may not have hyperadrenocorticism.

References

Reference available on request.