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WHAT TESTS SHOULD I RUN?

The minimum database is a CBC, biochemical profile and urinalysis. A T4 should be performed in patients older than 5 years of age. There is no proven cause-and-effect relationship between hypothyroidism and seizures, but there are anecdotal reports suggesting that hypothyroidism may exacerbate seizures making them more difficult to control. Phenobarbital administration lowers both total T4 and free T4 leading to a subsequent increase in TSH making it difficult to determine whether or not a patient that is receiving phenobarbital is truly hypothyroid. Therefore, a total T4 level should be obtained in older patients prior to starting phenobarbital. Bile acids testing should be performed in all patients to rule out a portosystemic shunt (PSS) and to obtain a baseline prior to starting phenobarbital. It is important to remember that the CBC/biochemical profile can be normal even in patients with PSS so a bile acids test should still be performed. I’ve diagnosed many middle-aged patients with PSS who present for seizures or other neurological signs with normal liver values. Blood lead levels should be performed if the owner’s house was built prior to 1978, especially if there’s a reasonable risk of lead exposure (flaking paint, recent remodeling, etc.), or if there are CBC changes consistent with lead exposure (e.g., nucleated red blood cells, basophilic stippling). If initial diagnostics are normal, then the next step would be brain imaging (MRI > CT) and cerebrospinal fluid (CSF) analysis. Advanced imaging is highly recommended for any patient younger than 1 year of age or older than 5 years of age, if seizures are refractory to standard anticonvulsants, or if there are any neurological signs between seizures.

WHEN SHOULD I START TREATMENT?

There is no hard and fast rule. Frequent seizures require treatment, but how frequent is frequent? Chronic, repetitive seizures cause microscopic changes that make it more likely to have seizures (“Kindling phenomenon”). As a result, I typically start anticonvulsants if there is more than 1 seizure every 6 months.

An anticonvulsant should also be started immediately for any unprovoked status epilepticus or cluster seizures, if there is a trend towards increasing frequency, or if there is a known structural cause for the seizures (e.g., brain tumor).

Client education is extremely important prior to starting an anticonvulsant. I often talk to clients about how treatment is a team effort between the veterinarian and family members. It is important that they understand that anticonvulsants may need to be given for life and that it is critical that they give the anticonvulsants as directed. They also must be informed of the cost of treatment and therapeutic monitoring. If they do not buy in to the treatment plan, then failure is almost certain.

HOW MANY SEIZURES ARE ACCEPTABLE TO BE CONSIDERED “WELL CONTROLLED?”

Again, there is no hard and fast rule. My goal is always to completely eliminate all seizure activity, but that is uncommon and not realistic. Treatment involves achieving a balance between seizure control and side effects of medication(s). For dogs & cats with Idiopathic Epilepsy (i.e., no underlying structural disease that makes seizure control more difficult), I typically try to reduce seizure frequency to no more than one short seizure every three months. A recent study that looked at quality of life
and life span of seizure patients on phenobarbital and/or potassium bromide found that most owners consider one seizure every three months to be adequate seizure control with a good quality of life.

WHAT IS THE PROBABILITY OF TREATMENT SUCCESS?

Approximately 75-80% of dogs with Idiopathic Epilepsy can be well controlled with one or two anticonvulsants. The other 20-25% of dogs are more difficult to control, and are on three or more anticonvulsants. These statistics are similar in human medicine. It is equally important for both our patients and their owners to have a good quality of life. A balance between seizure control and side effects must be achieved with the owner’s help. Ultimately, it is often the owners that guide me in how aggressive I am in trying to control the seizures. In some patients with very frequent seizure activity and/or significant side effects, I am happy to get to one seizure per month as long as the client is happy.

WHICH ANTICONVULSANT SHOULD I USE?

The standard first drug for dogs is either phenobarbital or potassium bromide (KBr). For cats, the first anticonvulsant is phenobarbital. Which one I choose is based on a number of factors, such as age of the patient, suspected underlying cause of seizures, and length of treatment that will be required. I typically reach for phenobarbital in cases where seizures are frequent and/or severe, due to its rapid onset of action. It is also my first line drug for older patients with a structural brain disease. I start with KBr if the seizures occur less often than one per month. If seizures are more frequent, I load the patient prior to starting the maintenance dose of KBr. Phenobarbital requires monitoring every six months, which significantly increases the overall cost of treatment compared to other anticonvulsants. In addition, many owners are aware of the possibility of hepatotoxicity and are reluctant to use the medication. Although the incidence of hepatotoxicity is low (probably less than 1% of cases), it can be severe and possibly life-threatening. As a result, I have been using phenobarbital less frequently, especially in younger patients who will be on anticonvulsants long term. Some of the newer anticonvulsants are now available as generics, are more cost effective for owners and have fewer short term side effects (long term adverse reactions have not been reported yet). These factors are inducing many neurologists to use zonisamide and levetiracetam (generic version of Keppra) as the first anticonvulsant for some patients. I have found Costco’s pharmacies to be significantly cheaper than most of the national pharmacy chains; the medication cost at Costco is often half the price of the national chains. They also offer online ordering and shipping.

WHEN AND HOW SHOULD I MONITOR ANTICONVULSANTS?

When to monitor anticonvulsants depends on the time needed to reach steady state levels. For first pass elimination medications, steady state is achieved at about five times the elimination half-life. For phenobarbital, zonisamide, and levetiracetam, ideally a CBC/biochemical profile should be performed one month after starting the medication to look for any systemic/metabolic derangements. For all three of these medications, steady state is reached by two weeks and a serum level can be checked at that time. KBr has a long elimination half life (dogs about 25 days, cats about 10 days) so steady state levels may not be reached for 3-4 months.

Therapeutic monitoring should be performed in the following circumstances:

1. When steady state levels have been reached after starting or changing the dose of an anticonvulsant. Serum anticonvulsant levels can be checked immediately after completing a loading regimen.
2. When there are signs of dose-related toxicity.
3. When seizures are not well controlled, to help determine whether an additional anticonvulsant should be started.
4. Every 6-12 months depending on the anticonvulsant for routine monitoring.

Practical tips

1. Ideally, a trough level should be obtained, but this is not practical for many clients due to timing of medication administration. A recent study showed that the time of day a serum phenobarbital level was drawn had little effect on the decision to alter dose in approximately 90% of patients.
2. Peak and trough anticonvulsant levels may help estimate the half-life and determine whether a medication should be given more often.
3. Treat the patient, not the lab test results. Some patients may be well controlled with “sub-therapeutic” levels. Other patients may need to have their serum concentration higher than the therapeutic range would suggest, as long as there are no significant side effects. The exception would be phenobarbital.
4. “Therapeutic levels” are often approximations based on retrospective studies or small pharmacokinetic

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MEDICATION FAQS:

PHENOBARBITAL

Mechanism of action: Phenobarbital acts on the GABAA receptor to increase the length of time the chloride channel is open.

Standard dose: 2 mg/kg PO BID starting dose; loading dose: 16-20mg/kg total dose divided. I personally give 4mg/kg IV every 4 hours for 4 doses (easy to remember: 4-4-4). The daily maintenance dose should be based on serum phenobarbital levels. Autoinduction of liver enzymes often leads to the need for increasing the dose over time.

Time to steady state level: 10-14 days

Therapeutic level: 15-40 µg/mL. Levels greater than 35 µg/mL increase risk of hepatotoxicity.

Metabolism: Liver

Adverse effects: Short-term side effects include sedation/lethargy, weakness and ataxia. These usually resolve in 2-3 weeks. Long-term side effects include PU/PD, polyphagaia and weight gain. Serious adverse effects include blood dyscrasias (neutropenia, anemia, thrombocytopenia), rare hepatocutaneous syndrome and hepatotoxicity.

Notes: Phenobarbital causes autoinduction of liver enzymes. Mild to moderate increase in ALP and mild increase in ALT are possible. Bile acids testing should be performed every six months or if there are any clinical or hematological signs of hepatotoxicity, such as a disproportionate increase in ALT compared to ALP, hypoalbuminemia, low BUN, low cholesterol, etc. I recommend a CBC/biochemical profile/T4, serum phenobarbital level, and bile acids test every six months.

BROMIDES (potassium bromide, sodium bromide)

Mechanism of action: It is thought the bromide competes with chloride at the neuronal membrane leading to membrane hyperpolarization which increases the seizure threshold.

Standard dose: Many different starting doses for KBr have been published. If it is the sole anticonvulsant, I start at 40-50 mg/kg/day. If added to other anticonvulsants, I start at 20-30 mg/kg/day. There are also many published loading doses. I usually give 400-600 mg/kg as a total dose divided over 2-4 days depending on frequency/severity of seizures. If NaBr is used, decrease the dose calculated for KBr by 15% to obtain the NaBr dose. **DO NOT USE IN CATS** – may cause pneumonitis which can be severe and possibly life-threatening.
**Time to steady state level:** 3-4 months for dogs (elimination half-life is 20-25 days) and 6 weeks for cats (elimination half-life is 10 days)

**Therapeutic level:** 1-3 mg/mL

**Metabolism:** Bromide is excreted unchanged by the kidneys. Patients with isosthenuria or azotemia should be given a lower dose and the serum bromide level monitored closely.

**Adverse effects:** Short-term side effects include sedation/lethargy, weakness and ataxia. These usually resolve in 2-3 weeks. Long-term side effects include PU/PD, polyphagia and weight gain. Pancreatitis is possible, especially in combination with phenobarbital, but it is unclear if this is due to the medications themselves or related to side effects of polyphagia and indiscriminate eating.

**Notes:** There is no significant difference in efficacy between KBr and NaBr. Potassium bromide should be avoided where increased serum potassium levels are contraindicated (e.g., hypoadrenocorticism). NaBr should be avoided in patients with cardiac disease. I prefer using liquid KBr over pills/capsules because it is easier to change the dose. I also divide the daily dose into BID dosing to decrease nausea/vomiting. I instruct owners to mix the medication into the food or squirt on a piece of bread. Giving the medication directly by mouth is more likely to cause nausea/vomiting and patients do not tolerate it well. Bromide competes with chloride for elimination by the kidneys. High salt diets lead to excessive bromide elimination into the urine and lowered bromide blood levels. As a result, high and low salt diets should be avoided. Many laboratory machines are unable to distinguish chloride from bromide leading to falsely elevated chloride levels.

**LEVETIRACETAM (generic Keppra)**

**Mechanism of action:** Not completely understood – may prevent hypersynchronization of epileptiform burst-firing and propagation of seizure activity

**Standard dose:** 20mg/kg PO TID

**Time to steady state level:** 2 days

**Therapeutic level:** Lab uses 5.5 – 21 µg/mL

**Metabolism:** 70-90% excreted unchanged by the kidneys, remainder is hydrolyzed in serum and other organs.

**Adverse effects:** Mild transient sedation, decreased appetite in cats

**Notes:** Since the liver does not metabolize levetiracetam and it reaches steady state levels quickly, this is a good anticonvulstant to use in patients with liver dysfunction. The elimination half-life is approximately five hours in dogs and three hours in cats. This would suggest that the medication would need to be given more frequently than TID. However, its clinical effect seems to last longer allowing TID dosing. Note that the therapeutic level above is extrapolated from human medicine and small veterinary pharmacokinetic studies; it should be used as a rough guide only.

**ZONISAMIDE**

**Mechanism of action:** Not completely understood – blocks voltage-dependent sodium channels, as well as T-type calcium channels

**Standard dose:** 5-10mg/kg PO BID

**Time to steady state level:** 3-4 days

**Therapeutic level:** Lab uses 10-40 µg/mL

**Metabolism:** Hepatic microsomal enzymes

**Adverse effects:** Mild transient sedation, decreased appetite

**Notes:** Zonisamide is a sulfonamide derivative. It should not be used in patients with a sulfa allergy. Note that the therapeutic level above is extrapolated from human medicine and small pharmacokinetic studies; it should be used as a rough guide only.

**GABAPENTIN**

**Mechanism of action:** Not completely understood – inhibits calcium flow by binding to neuronal voltage-gated calcium channels

**Standard dose:** 10mg/kg PO TID starting dose

**Time to steady state level:** 1-2 days

**Therapeutic level:** Not performed

**Metabolism:** Partially metabolized by the liver; remainder excreted by kidneys

**Adverse effects:** Mild transient sedation and ataxia

**Notes:** Do not use the human oral solution because it contains xylitol.

**FINAL NOTES**

Many other anticonvulsants exist, such as topiramate, felbamate, and oral benzodiazepines. I’ve listed only the most common medications above. Most of the human anticonvulsants can’t be used in veterinary medicine due to either a very short half-life or toxic byproducts. Felbamate is a safe medication, but studies have shown that there is a higher risk of hepatotoxicity when used in conjunction with other liver metabolized medications. Topiramate (Topomax) is being used more often in veterinary neurology for refractory seizures. Oral benzodiazepines are very effective, but tolerance to the medications is common.
UROLITHIASIS REFERS TO THE FORMATION OF STONES anywhere within the upper and lower urinary tracts. It is a common problem among both canine and feline patients in veterinary medicine and one of the most common causes of lower urinary tract signs. Urolithiasis is not a disease entity in itself, but rather a clinical consequence of several different disease entities. Determining the make-up of the urolith will help give clues into the causes, treatment and prevention of further urolith formation. There are no protocols to help promote dissolution of calcium oxalate uroliths so they have to be physically removed.

In a recent review of all stones submitted to the Minnesota Urolith Center, Calcium Oxalate stones represented 42% of all stones submitted. It is now the second most common cause of stones in both dogs and cats. Dogs that are affected with calcium oxalate urolithiasis are typically middle aged to older male small breed dogs. Affected cats are typically middle-aged to older male or female cats.

CAUSES

The cause for formation of calcium oxalate urolithiasis is incompletely understood and may be multifactorial. Both hypercalciuria and hyperoxaluria can predispose to calcium oxalate stone formation. Hypercalcemia promotes hypercalciuria which may lead to formation of calcium oxalate stones. Approximately 35% of cats and 4% of dogs with calcium oxalate urolithiasis were hypercalcemic. Ionized calcium should be always be checked in animals with calcium oxalate urolithiasis for elevations, even with a normal total calcium. In one study of cats with hypercalcemia, 25% had normal total calcium and only ionized hypercalcemia. The most common cause of hypercalcemia in cats with calcium oxalate urolithiasis was idiopathic hypercalcemia, while the most common cause in dogs was primary hyperparathyroidism. Other causes of hypercalciuria could include excessive dietary calcium, animal protein and/or vitamin D consumption, medications that cause calcium elimination in the urine (furosemide, prednisone), vitamin B6 deficiency, hyperadrenocorticism, metabolic acidosis and excessive oxalate excretion from excessive dietary intake of oxalate and/or ascorbic acid.

DIAGNOSIS

Radiography is the cornerstone for diagnosis of urolithiasis. Calcium oxalate uroliths are radioopaque, so they are easily seen on abdominal radiograph when greater than 2-3mm in diameter. Pneumocystography (negative contrast cystography) is more sensitive at detecting bladder stones than regular radiography, with a false negative rate of 6.5%. Adding a small amount of contrast and performing a double-contrast cystography improves accuracy with a false negative rate of 5%. Ultrasound is as sensitive as double contrast radiography for detection of bladder stones but is not useful for further characterization of number and/or size of stones.

TREATMENT

Voiding urohydropropulsion is a technique that can be used to evacuate uroliths of a small to moderate size (<5-7mm in diameter, depending on the size and sex of the patient). The patient is placed under general anesthesia and a catheter is advanced through the urethra into the bladder. Sterile saline is injected into the catheter to distend the bladder. The degree of bladder distension is assessed by abdominal palpation. Once the bladder is appropriately distended, the patient is repositioned so the spine is approximately vertical. This will cause the uroliths to fall into the trigone of the bladder. The bladder is agitated at this time to facilitate movement of the stones. Steady constant pressure is applied to the bladder to induce urination, and once urination starts, the bladder is more vigorously expressed until it is empty. The stream of urine can be caught and assessed for stone expulsion. This process may be repeated until all stones are flushed out. Double contrast cystography is advised at the end of this procedure to ensure no small stones are left.
Voiding urohydropulsion can be used as a sole therapy for removal, or can be used in addition to other therapies. This procedure is generally very safe when the correct technique is performed in a good candidate. The most common complications of voiding urohydropulsion is visible hematuria. Urethral obstruction with uroliths can occur during voiding urohydropulsion. If this should occur, the ureterolith should be flushed back into the bladder and removed via cystotomy or cystoscopy, if possible. Ruptured bladder is an uncommon risk of voiding urohydropulsion. This procedure should not be used in dogs or cats with urinary tract infections, urethral obstructions, or history of recent bladder surgery. This procedure can be performed as a sole therapy, or in conjunction with cystoscopy +/- lithotripsy.

Cystoscopy +/- laser lithotripsy can also be used for stone removal. Cystoscopy is performed with the patient under general anesthesia. This procedure is ideal for a single to a few larger stones. Once the stones are visualized, a basket is passed under cystoscopic guidance. The basket is placed around the stone, and then the entire apparatus is removed. This procedure is most useful in female cats for stones 3-5mm and female dogs for stones 4mm-1cm varying on the size of the dog. In male dogs, due to the small diameter and longer length of their urethras, this can be attempted for few stones 2-3mm in diameter. For stones that are larger than this, laser lithotripsy can be performed under cystoscopic guidance and the fragments can be removed via stone baskets with cystoscopy, or via voiding urohydropulsion.

Percutaneous cystolithotomy is a new technique used to remove stones from the bladders of dogs and cats. This method is performed via a small ventral midline skin incision made directly over the bladder. A trocar is advanced into the bladder lumen and a rigid cystoscope is advanced through the trocar into the urinary bladder. Stone removal is performed with an endoscopic stone basket. The advantages of this technique are that the entire mucosal surface of the bladder and the urethra can be evaluated with high powered magnification of the cystoscope. After the stones are removed the bladder is closed and the skin incision is closed. This procedure can be performed on an outpatient basis. A recent article(J Am Vet Med Assoc. 2011 Aug 1;239(3):344-9) evaluated the use of PCCL in a population of dogs and cats with cystoliths. In that population of 27 animals, the median procedure time was 66 minutes, and no complications were noted.

Routine cystotomy is also a reasonable alternative for stone removal, especially with a large number of stones or multiple very large stones. In a recent study (J Am Vet Med Assoc. April 2010;236(7):763-6), 20% of dogs had incomplete removal of bladder stones via cystotomy. Performing post-operative radiographs (ideally a double contrast cystogram) is considered standard of care to help prevent this occurrence.

**PREVENTION**

Risk factors that promote hypercalciuria and oxaluria should be addressed.

Since urolith recurrence is very common, follow-up radiographs every 2-3 months for the first year, then every 3-6 months thereafter to look for recurrence of stones. If small stones are found early, they can be removed by voiding urohydropulsion and prevent the need for an additional surgical procedure.

Increased water intake is essential to decrease the risk of recurrent urolithiasis. This can be accomplished by feeding a canned food diet and encouraging water consumption. Urinalysis should be monitored for urine specific gravity, calcium oxalate or struvite crystalluria and/or signs of inflammation every 3-6 months. Ideally, urine pH should be maintained between 6.8 and 7.2 and urine specific gravity should be less than 1.020.

Diets for dogs with calcium oxalate uroliths should contain citrate as well as have adequate phosphate and magnesium. Commercial diets that have most frequently been advocated for prevention of calcium oxalate urolithiasis include Royal Canin SO and Hill’s Prescription Diet u/d. Diets with a high fat content such as u/d should be avoided in dogs with a history of pancreatitis, obesity, diabetes mellitus or hyperlipidemia. Alternative diets that are lower in fat include Hill’s w/d or Hill’s g/d. These low-fat diets should be supplemented with oral potassium citrate. Excessive vitamin C and vitamin D intake should be avoided. Vitamin C can be broken down by the body into oxalates, increasing the risk for calcium oxalate stones. Vitamin D will increase the risk of calcium oxalate stones by increasing the excretion of calcium into the urine.

Deficiency of Vitamin B6 promotes endogenous production and excretion of oxalates, so B6 supplementation may also be advocated in these cases, especially if a home-made diet is used. For dogs with a history of calcium oxalate stones, potassium citrate (75-100mg/kg BID) may be helpful to minimize oxalate
Calcium Oxalate Urolithiasis

excretion. Thiazide diuretics have also been shown to lower calcium oxalate supersaturation in the urine and theoretically can be used to decrease the likelihood of calcium oxalate stone formation if the above therapies are not effective. Thiazide diuretics promote calcium retention, so they are contraindicated if hypercalcemia is a contributing factor.

New therapies that are currently being investigated for prevention of calcium oxalate urolithiasis include probiotics. Oxalobacter formigenes is a non-pathogenic intestinal anaerobic microbe that ingests oxalates as its sole nutrient. With more oxalate removed in the intestine, less oxalate is available for absorption into the bloodstream, decreasing blood and urine oxalate concentrations. Oxalobacter formigenes have shown to decrease urinary oxalate levels in humans, but no clinical studies have yet been conducted in veterinary medicine. Other intestinal bacteria can also metabolize intestinal oxalate.

Calcium oxalate urolithiasis is a frustrating problem for both clients and owners, with a recurrence rate approaching 50% within three years of initial diagnosis. With measures to decrease risk of recurrence and careful monitoring, if recurrences happen they can be managed using less invasive techniques, voiding urohydropulsion, or cystoscopic guided stone retrieval.

### FIGURES AND TABLES FOR CANINE HYPOADRENOCORTICISM - WHAT WE KNOW AND HAVE LEARNED

![Regulation of Aldosterone Secretion](image)

**Fig. 1: Regulation of Aldosterone Secretion**

<table>
<thead>
<tr>
<th>Increased Risk</th>
<th>Decreased Risk</th>
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<tr>
<td>Standard Poodle</td>
<td>Boxer</td>
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<td>Portuguese Water Dog</td>
<td>Cocker Spaniel</td>
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<td>Nova Scotia Duck Trolling Retriever</td>
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<td>Wheaten Terrier</td>
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*Table 1: Breeds reported to be either at increased or decreased risk of hypoadrenocorticism*
HYPOADRENOCORTICISM IS A LIFE-THREATENING disease and is a result of failure of the adrenal glands to produce adequate hormones. Eighty-five percent of both adrenal glands have to be destroyed in order for clinical signs to occur. Most commonly deficiency of both mineralocorticoid and glucocorticoid hormones is present, however an atypical form also occurs where deficiency of glucocorticoid hormones alone causes significant disease. In humans, Thomas Addison first described hypoadrenocorticism in 1855 where necropsies showed complete destruction of the adrenal glands in patients with clinical signs now associated with this disease. The first case of hypoadrenocorticism in dogs was described in 1953 and in cats in the 1980s.

PHYSIOLOGY AND ETIOLOGY OF HYPOADRENOCORTICISM

The cortex of the adrenal gland has three zones and of these zones, two of them are important in the function of the adrenal gland. The outer zone – zona glomerulosa – secretes aldosterone and the next zone – zona fasciculata – secretes glucocorticoids. The most inner zone – zona reticularis – secretes sex hormones and they do not contribute to signs associated with hypoadrenocorticism. Aldosterone promotes sodium, chloride and water resorption, and potassium excretion in epithelial tissues. The primary site of effect is the renal tubule (proximal convoluted), however other tissues where an effect is exerted include the intestinal mucosa, salivary glands and sweat glands. Secretion of aldosterone itself is controlled by the renin-angiotensin system where angiotensin II is ultimately produced and acts directly on the adrenal gland to produce aldosterone (See Figure 1, page 8). Other stimulants of aldosterone include potassium through a transmembrane effect as well as, to a much lesser extent, ACTH hormone. Glucocorticoids are produced as a result of increased stress and ACTH secreted by the pituitary gland in response to corticotropin-releasing hormone (CRH), as well as cortisol metabolism. Cortisol affects almost every tissue in the body. Some of its actions include the effects on the vascular system, such as maintaining vascular tone; effects on metabolism such as stimulating gluconeogenesis and glycogenolysis; control over hormone release including ACTH, CRH, and vasopressin; control of the immune system by suppressing inflammatory response; stimulating erythrocytosis.

The cause of primary hypoadrenocorticism is most commonly thought to be immune-mediated destruction of the glands. Other causes include granulomatous disease seen with histoplasmosis or blastomycosis, hemorrhagic infarctions which can be seen with rodenticide toxicity or trauma, metastasis such as lymphoma, as well as amyloidosis. Iatrogenic causes can include surgery, treatment with Trilostane or Lysodren as well as rapid withdrawal of corticosteroids. Secondary hypoadrenocorticism usually is seen along with other neurologic and ophthalmologic signs and is caused by a primary deficiency of ACTH, as a result of lack of pituitary production or secondary deficiency of CRH production from the hypothalamus. Neoplasia, trauma and inflammation are common causes.

SIGNALMENT AND CLINICAL SIGNS

Dogs diagnosed with this disease are usually young to middle-aged and 69% are female. Mixed breed dogs are most commonly diagnosed, however there are breeds at higher risk for developing Addison’s disease. (See Table 1, page 8).

There are no pathognomonic signs with hypoadrenocorticism and this disease is known as the great mimicker. It mimics signs seen with kidney, gastrointestinal (GI) and some infectious diseases. The signs can be waxing and waning or episodic but this occurs only in about 25% of dogs. Signs can include anorexia, lethargy, weight loss, weakness, vomiting or diarrhea, but can be as severe as collapse. Physical exam findings can also vary but can include weakness, thin body condition score, dehydration, shock, hypothermia, bradycardia, hypotension, and evidence of melena or hematochezia on rectal exam.

BASELINE DIAGNOSTIC TESTING

In patients with hypoadrenocorticism, a complete blood count may show normocytic, normochromic anemia (Hct 20-35%) secondary to bone marrow suppression from chronic hypocortisolism and this may not become apparent until the patient is rehydrated. Anemia may be significant especially in those patients with GI hemorrhage. Classically the complete blood count will lack a stress leukogram with a lymphocytosis and eosinophilia predominating. A----bout 80% of patients with hypoadrenocorticism will have normal leukocyte counts. This finding alone should raise the
Canine Hypoadrenocorticism – An Overview Of What We Know And Have Learned

suspicion for hypoadrenocorticism.

On chemistry profile, hyponatremia and hyperkalemia are classically found due to the lack of aldosterone production. A ratio below 27:1 should start to raise suspicion for hypoadrenocorticism, it has been found that a ratio of 24:1 is highly specific for the diagnosis. Other diseases can cause these electrolyte abnormalities - for examples please refer to tables 2 and 3. It is important to remember that these electrolyte changes are not always present in patients with hypoadrenocorticism. In atypical hypoadrenocorticism electrolytes will be normal. Other possible causes for hypoadrenocorticism with normal electrolytes include pituitary ACTH deficiency, lysodren or trilostane induced hypocortisolemia, or concurrent illness. Up to 30% of animals diagnosed with hypoadrenocorticism can have normal electrolytes. Increased BUN can be found especially in cases of dehydration, intestinal bleeding as well as an increased creatinine due to reduced renal perfusion. Urine specific gravity may be reduced due to impaired ability to concentrate urine due to chronic urinary sodium losses, medullary washout, impaired capacity for water resorption. Evidence of hepatic dysfunction may be present via hypoalbuminemia, hypoglycemia and hypocholesterolemia. Liver function testing may be slightly abnormal. Hypercalcemia and mild to moderate metabolic acidosis are also possible findings, especially the latter due to reduced tissue perfusion and impaired hydrogen excretion.

In animals with hypoadrenocorticism, thoracic radiographs may reveal megaesophagus as well as a flattened aorta and narrow posterior vena cava. The mechanism of megaesophagus is unclear. It is thought that this may be related to the effect of abnormal serum sodium and potassium concentrations on neuromuscular functions, or the lack of cortisol having an effect on muscle function.

Abdominal ultrasound findings include small adrenal gland size, although normal sized adrenal glands do not exclude hypoadrenocorticism as a diagnosis. In addition to this, evidence of more rare causes of hypoadrenocorticism may be found such as metastasis or granulomatous disease.

In some cases of hyperkalemia an EKG is indicated and possible findings include a slowed heart rate, peaked T–waves, widened QRS complex, and as potassium increases, one can diagnose an increased P-R interval, lack of p-wave, progressing to ventricular asystole or ventricular fibrillation.

ENDOCRINE TESTING

Baseline cortisol concentrations can be used in some patients where hypoadrenocorticism is a suspicion. A cortisol concentration greater than 2 ug/dL is known with a 100% sensitivity to exclude the diagnosis of hypoadrenocorticism. However if the concentration is below 2 ug/dL, an ACTH stimulation test is needed to confirm the diagnosis.

The gold standard, and most commonly used method to diagnose hypoadrenocorticism, is an ACTH stimulation test where both pre and post values should be less than 2ug/dL. This test does not distinguish primary versus secondary hypoadrenocorticism. To differentiate between these two an endogenous ACTH concentration can be submitted (careful handling instructions necessary) where a low concentration is diagnostic of secondary hypoadrenocorticism. To perform the ACTH stimulation test synthetic ACTH is administered. A dose of 5ug/kg given intravenously or intramuscularly is a sufficient dose (max dose 250 ug/dog) with a post sample taken one hour after ACTH administration. It has recently been documented that there is no difference between the use of the lyophilized ACTH product intramuscularly and the liquid ACTH product given intravenously. If steroids need to be given prior to performing the ACTH stimulation test, it is important that Dexamethasone is

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal</td>
<td>Renal failure, urinary obstruction, rupture of urinary bladder</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Parasitism [e.g. trichuriasis], other infection [salmonellosis, parvovirus], perforated ulcer, severe malabsorption; liver failure</td>
</tr>
<tr>
<td>Severe acidosis</td>
<td>Pancreatitis, trauma, DKA, heat stroke</td>
</tr>
<tr>
<td>Effusions</td>
<td>Repeated drainage of pleural or abdominal effusion; heart failure</td>
</tr>
<tr>
<td>Iatrogenic</td>
<td>Hemolyzed blood samples, extreme leukocytosis or thrombocytosis, akitas (large amount of potassium in red blood cells)</td>
</tr>
</tbody>
</table>

Table 2: Causes of hyperkalemia

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary</td>
<td>Renal tubular diseases, nephrotic syndrome, postobstructive diuresis</td>
</tr>
<tr>
<td>Osmotic diuresis</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Parasitism, ulcerative disease, viral disease</td>
</tr>
<tr>
<td>Edema, effusions</td>
<td>Heart failure, repeated drainage of effusion</td>
</tr>
<tr>
<td>Primary polydipsia</td>
<td></td>
</tr>
<tr>
<td>Syndrome of inappropriate ADH secretion</td>
<td></td>
</tr>
<tr>
<td>Iatrogenic</td>
<td>Lipemic blood sample, low salt diet</td>
</tr>
</tbody>
</table>

Table 3: Causes of hyponatremia
used. Dexamethasone is not detected by cortisol assays and it has minimal effect on the post-ACTH cortisol concentration.

**TREATMENT** (see Table 4 for doses)

Emergency treatment is often indicated in animals due to severe dehydration, hypotension and electrolyte abnormalities. Saline boluses should be used although care should be given not to rapidly correct sodium blood concentrations as cerebral myelitis may result. Glucocorticoids should be administered and dextrose should be given to treat hypoglycemia and help counteract hyperkalemia. If hyperkalemia is significant and life-threatening, one should also consider treating with insulin to lower potassium and calcium gluconate to protect the myocardium. DOCP may be given if there is strong clinical suspicion however ideally results of the ACTH stimulation test should be available.

Maintenance therapy will be tailored to each individual patient. Prednisone should be administered with every patient having the dose tapered to lowest dose that will control signs and avoid side effects. In some patients every other day prednisone dosing is adequate. It is important to increase dosage during times of stress by doubling the dose of steroid that the patient is getting for about one week after stress and then taper again over 2-4 weeks. In those patients where electrolyte abnormalities are diagnosed mineralocorticoid hormone supplementation is required. Desoxycorticosterone Pivalate (DOCP, Percorten V) is the most common drug used to supplement mineralocorticoids. Initially, electrolytes should be reevaluated one week after discharge, then at 14 and 25 days to assess electrolyte control and DOCP dose as well as interval needed between injections. At 14 days electrolytes should be normal and if they are not, the dose of DOCP should be increased by 5-10%. At day 25 electrolytes should be evaluated and the interval changed based upon control of electrolytes. When the interval appears to be greater than 30 days administration, the dose can be decreased by 10% at each dosing but careful electrolyte monitoring is necessary. After the first 2-3 months if an appropriate dose and interval is achieved owners can be shown how to administer the injection, and re-evaluation every 3-6 months should be scheduled. Fludrocortisone Acetate (Florinef) can be used in place of DOCP if daily oral therapy is preferred. In some cases, when Florinef is used, prednisone therapy can be discontinued completely as it may have enough glucocorticoid therapy. However, some patients also may have severe glucocorticoid side effects and in those cases a switch to DOCP may be necessary. Electrolytes for patients using Florinef should be monitored weekly to every two weeks until electrolytes are stable, although continued monitoring 2-3 times per year is needed as increased dosing in first 6-18 months of treatment is often necessary. If it is determined that a switch to DOCP from Florinef is needed, then it is recommend to taper Florinef over 4-5 days beginning on the day that DOCP is given. Hydrocortisone is not good option for long term management of electrolytes as a high dose would be needed to get enough mineralocorticoid effect, and likely significant glucocorticoid side effects would be noted.

In those patients where electrolyte abnormalities are not noted, treatment with only prednisone is necessary. It is recommended however that electrolytes be monitored every 1-3 months at least for the first year post diagnosis. Owners should monitor for any signs of illness as certain patients do develop electrolyte abnormalities after initially being normal.

In general the prognosis for patients diagnosed with hypoadrenocorticism is excellent with a reported median survival time of 4.7 years. If poor response to therapy is noted electrolyte control should be evaluated as well for other underlying concurrent illnesses.

<table>
<thead>
<tr>
<th>Drugs &amp; Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Emergency</strong></td>
<td></td>
</tr>
<tr>
<td>Fluids</td>
<td>Saline boluses 20-30 ml/kg</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>Dexamethasone 0.25-2 mg/kg, Hydrocortisone 1.25 mg/kg, followed by 0.5 mg/kg q 6hrs during first day</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>50% Dextrose 1 ml/kg, Insulin 0.5 u/kg, Calcium gluconate 10% 0.5-1 mg/kg over 10-20 minutes</td>
</tr>
<tr>
<td>Gastrointestinal protectants</td>
<td>Pepcid 0.5 -1 mg/kg SID, Carafate 0.25 -1 g TID</td>
</tr>
<tr>
<td><strong>Maintenance</strong></td>
<td></td>
</tr>
<tr>
<td>Glucocorticoid</td>
<td>Prednisone at 0.1-0.22 mg/kg</td>
</tr>
<tr>
<td>Mineralocorticoid</td>
<td>Desoxycorticosterone Pivalate (DOCP, Percorten V by Novartis) 2.2 mg/kg IM or SQ q 25 days [can vary 0.8-3.4 mg/kg/dose from 14-35 days]</td>
</tr>
<tr>
<td></td>
<td>Fludrocortisone/Florinef (0.1 mg tablets) 0.02 mg/kg/day - single or divided dosing (Dose can range from 0.01 to 0.08 mg/kg/day)</td>
</tr>
</tbody>
</table>
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References for all articles available upon request.