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Monitoring during Vetoryl® therapy, Diagnosing Morbus Addison – A diagnostic challenge

An ACTH stimulation test is considered the gold standard for the diagnosis of Morbus Addison and therapy control of Cushing's disease patients on Vetoryl® (active component: Trilostane). Unfortunately, ACTH (Synacthen®) has been removed from the market. Diagnosis and therapy control must therefore be based on other methods. This, despite the fact that the manufacturer of Vetoryl® states on the label that frequent controls using ACTH stimulation testing are necessary.
Vetoryl® treatment is begun using the lowest dose of 3 mg/kg body weight once daily.

Mode of action

Trilostane selectively and reversibly inhibits the enzyme system 3-β-hydroxisteroiddisomerase, which stops the synthesis of cortisol, corticosterone, and aldosterone. The side effects of an excessive level of medication can therefore be as diverse as the functions of the secreted hormones.

The most critical side effect is a low aldosterone level, since this can be fatal. Aldosterone is generally synthesized and secreted independently of the ACTH/corticosterone cycle. Synthesis and secretion are regulated via the renin-angiotensin system. Aldosterone synthesis is inhibited by Trilostane independent of the renin-angiotensin system. The resulting aldosterone deficit leads to hyperkalemia, which leads to bradycardia, hyponatremia, hypotonia, and reduced kidney perfusion with pre-renal azotemia.

Clinically, these patients become apathetic and lose weight. These signs are easily noticed by owners, but can be difficult to interpret, particularly at the beginning of treatment with Vetoryl®, especially since weight loss is often desired and apathy is observed in many patients with Cushing's disease. In cases in which Cushing's disease is not clearly diagnosed, therapy with Vetoryl® should not be attempted, as one could risk inducing an Addisonian crisis.

In case of a suspected Cushing's disease with a therapy resistant diabetes mellitus it is very important to carefully consider if and how Vetoryl® therapy should be initiated.

Because of the pleiotropic effects of corticosteroids, changes in physiological secretion are associated with multiple changes in metabolism. These include the glucose, protein, and fat metabolisms, the immune system, the mineral balance (weak effect of mineral corticoids on Na and K), and the Ca balance. Other endocrine systems are also influenced by corticosteroids. This leads to a diverse clinical picture in both absolute and relative decreased cortical levels. Which again leads to reduced stress tolerance, excessive immune reactions, delayed adjustments in the glucose balance and therefore in the energy metabolism.

Monitoring Vetoryl® therapy

Without ACTH stimulation testing, a number of parameters must be used to evaluate the success of therapy and these become extremely important.

In addition to the parameters that can be measured and evaluated by the owner such as amount of water consumed, amount of urine voided, changes in weight, appetite, vomitus and faecal consistency as well as weakness or apathy, measurement of heart rate, quality of pulse, capillary refill time, and skin turgor should all be included in the surveillance scheme.

It can be helpful to keep a therapy protocol (see attachment). This makes the evaluation of the current patient status compared to status prior to therapy begin easier. It is advantageous to always evaluate these parameters under the same conditions, for compatibility. Various laboratory parameters should also be examined regularly, like base cortisol level, electrolytes (sodium, potassium, and their ratio), as well as liver and kidney specific enzymes and substrates. These values provide valuable indications of a balanced therapy or warn against a life-threatening derail.

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Base Cortisol Levels

Measurement of base cortisol levels alone is not considered a sufficient measurement of Vetoryl® treatment efficacy by the manufacturer. However, it can be an important assessment criterion with additional parameters and can be crucial for the therapy going forward.
Since the time point of maximum suppression during Vetoryl® treatment is important, blood samples should be taken 2-5 hours after medication.
Control of the base cortisol level should be carried out in short intervals of 10 days, 28 days, 12 weeks, and every 3 months after beginning the therapy.

Cortisol <18 ng/ml:

According to the manufacturer's information, levels below this may be an indication of adrenal over suppression. The patient must be intensively evaluated and observed for clinical signs. As soon as signs of hypoadrenocorticism such as weakness, apathy, disorientation or vomiting with inappetence occur, Vetoryl® must be discontinued immediately.
Experience shows that base cortisol levels of <18 ng/ml can be found in previously conducted ACTH stimulation tests, even if the stimulation value following administration of ACTH is sufficiently increased. If the patient is clinically unremarkable and no critical changes are noted in laboratory testing, Vetoryl® therapy may be continued carefully with the same dose. If the clinical condition is not clear or distorted due to an overlying condition, discontinuation of Vetoryl® may be indicated as a cautious immediate action.

Base cortisol >18 ng/ml:

If the patient demonstrates a clear clinical improvement and laboratory parameters change to normal or closer to normal, therapy can be continued at the same dose.

If clinical signs of hyperadrenocorticism such as PU/PD persist even though the dog has been treated for 28 days with an adequate Vetoryl® dose, other causes of these clinical signs must first be ruled out.

After ruling out urinary tract infections, Diabetes mellitus or kidney disease, the Vetoryl® dose can be carefully increased

It generally takes longer for other clinical signs of Cushing's disease such as adrenocortical obesity, muscle atrophy, or hair loss to improve.

Cortisol/creatinine ratio from morning urine is unsuitable for therapy control.

Additional laboratory testing

Electrolyte concentrations

Changes in the sodium (Na), potassium (K), and chloride (Cl) concentration in serum indicate changes in aldosterone secretion and should therefore be checked regularly in order to be able to make a timely therapy adjustment.
This should also be done if the changes in the electrolyte concentrations may be due to other causes since an evaluation is difficult and the adrenal glands may not be able to adequately react to the situation under the influence of Vetoryl®.

Liver enzymes

If liver parameters are altered, these are expected to improve during Vetoryl® therapy. Do they not normalize or the concentration, particularly of alkaline phosphatase increases, can it, with correspondingly high cortisol concentrations, be necessary to increase the dose. If the overall liver parameters worsen during Vetoryl® treatment, even with sufficient cortisol concentrations, the dose should not be increased. Other causes of the changes in the liver values should be looked into.

Kidney parameters

Significant increases in the creatinine concentrations, even within the reference range, can indicate an over-suppression in patients undergoing Vetoryl® therapy.

The urea concentration should only be evaluated together with the creatinine concentration as this, in contrast to the creatinine concentration, is also dependent on protein metabolism and liver function.

Blood count

A stress leucogram is a change in the white blood cell count and includes a leucocytosis caused by neutrophilia, a lymphopenia, together with a mild monocytosis and eosinopenia.

Morbus Addison

The clinical results of a deficient production and secretion of glucocorticoids or mineralocorticoids by the adrenal glands are known as hypoadrenocorticism (Morbus Addison).

A **primary hypoadrenocorticism** is clinically dominated by a loss of production of all adrenal hormones. Are more than 90% of the tissue destructed, this leads to failure in the production and excretion of glucocorticoids and also mineralocorticoids. The cause is believed to be an immune mediated destruction of the adrenal cortex due to the formation of autoantibodies (idiopathic adrenocortical atrophy). Analogous to human medicine, dogs are believed to produce antibodies against the 21-hydroxylase, which play an important role in the synthesis of cortisol and aldosterone. A number of autoimmune mediated diseases such as hypothyroidism, Diabetes mellitus, and hypoparathyroidism are also associated with the formation of antibodies against the adrenal cortex. Especially young to adult intact female dogs (2 months to 4-6 years) are most commonly affected. Great Danes, Portuguese Water Spaniels, Rottweilers, Poodles, West Highland Terriers, and Soft Coated Wheaten Terriers are believed to have breed predispositions. Bearded Collies, Leonbergers, and Poodles are believed to have a genetic component, although the mechanism has not yet been elucidated.

Another cause of primary hypoadrenocorticism is the destruction of the adrenal cortex by medication. Approximately 5% of the dogs treated for Cushing's disease with Mitotane develop a complete irreversible destruction of the adrenal cortex. Glucocorticoids and mineralocorticoids must be substituted for life.

Treatment with Trilostane (Vetoryl®) can also lead to necrosis of the adrenal cortex and subsequently a Morbus Addison.
Other, rarer causes of a primary hypoadrenocorticism are bilateral adrenalectomy and destruction of the adrenal glands by tumours, infarcts, or amyloidosis.

A **secondary hypoadrenocorticism** is characterized by an insufficient production and secretion of ACTH followed by atrophy of the adrenal cortex and a decreased secretion of glucocorticoids. The most common cause is a persistent suppression of ACTH secretion in the pituitary gland caused by treatment with glucocorticoids, progesterone or megestrol acetate.
In this form of hypoadrenocorticism the concentration of mineralocorticoids (aldosterone) is almost unchanged, since their secretion is only minimally regulated by ACTH. Aldosterone is the "main mineralocorticoid" of the adrenal cortex. It stimulates the excretion of potassium in the kidney and causes reabsorption of sodium, chloride, and water, among others. Rare causes for secondary hypoadrenocorticism are tumours of the pituitary gland and/or the hypothalamus.

Clinical signs

The clinical signs are often unspecific and can be acute or occur intermittently over weeks and months. Clinical signs increase during stress. Phases in which the patient appears "sick" alternate with phases of good health. The cortisol deficiency leads to a decreased stress tolerance, resulting in inappetence, vomitus, diarrhoea, lethargy, and abdominal pain. Short term improvement is often observed after administration of corticosteroids. If additional aldosterone deficit is present, the clinical picture is dominated by lethargy, hypovolemia, hypotension, and bradycardia, decreased kidney perfusion, weakness, and muscle tremors as a result of sodium and water depletion as well as the hyperkalemia.

The most dramatic form of Addison's disease is an Addisonian crisis, in which a stress situation leads to an inadequate discharge of glucocorticoids and a reduced synthesis of mineralocorticoids. Animals are life-threateningly ill, and may collapse. They are bradycard with a weak pulse. These patients are absolute emergencies and may die without immediate substitution of mineralo- and glucocorticoids in conjunction with infusions.

Laboratory diagnostics show increased ACTH-concentrations (<500 pg/ml) in cases of primary hypoadrenocorticism due to the lack of negative feedback of cortisol in the pituitary gland. In contrast, dogs with a secondary hypoadrenocorticism have severely reduced or unmeasurable ACTH concentrations (<5 pg/ml). It is important to submit haemolysis free EDTA plasma for the measurement of ACTH.

Laboratory diagnostic comments:

Haematological and biochemical results can be as unspecific as the clinical signs.

Blood count:

The lack of a stress leucogram is an indication for hypoadrenocorticism in a sick, stressed animal.

Clinical chemistry:

Additional laboratory diagnostic indicators for Morbus Addison are an azotemia (increase in urea, creatinine, and phosphate) resulting from a decrease in kidney perfusion and a reduced glomerular filtration rate. The decrease in kidney perfusion is the result of hypovolemia, hypotension, and a reduced ventricular ejection. Vomitus and diarrhoea, water loss via the kidneys as well as inadequate water intake also support the development of a pre-renal azotemia. The specific gravity of pre-renal azotemic urine is generally relatively high (>1.030). In cases of hypoadrenocorticism, however, the kidney loses its ability to concentrate urine due to chronic sodium loss and the urine specific gravity (USG) sinks. Common findings in urinalysis are therefore USG values between 1.015 and 1.030. Rapid infusions lead to a reversal of the azotemic changes, an additional indication that the patient is suffering from a pre-renal azotemia. An increase in urea may result from gastrointestinal bleeding.

Electrolytes:

The most important laboratory diagnostic finding is a narrow Na-/K-ratio: A healthy dog has a ratio of >27:1 to 40:1, in an Addisonian patient, the ratio is <27:1 (<25:1). However, 10% of dogs with a primary hypoadrenocorticism have sodium and potassium levels within the reference ranges (atypical Addison's disease).
Haemolysis falsifies the potassium value, since potassium from the erythrocytes leads to increased levels. Differentials that should be ruled out include diseases which also cause changes in electrolyte concentrations (e.g. liver disease, kidney failure, gastrointestinal disease, blood loss, tumours).

Increases in calcium concentrations in cases of hypoadrenocorticism probably result from the interaction of reduced glomerular filtration, increased tubular reabsorption and hemoconcentration. In a study with 40 dogs, hypoadrenocorticism had caused hypercalcemia in 25%. Occasionally, dogs with Morbus Addison also have a reduced albumin concentration (6 to 39%). Intestinal bleeding, reduced synthesis in the liver, loss via the kidneys and a possible reduced absorption have been discussed as possible causes. Some Addison's patients also have a mildly increased AST and alkaline phosphatase (AP), possible results of reduced ventricular ejection and a reduced tissue perfusion.

Diagnosis without an ACTH stimulation test:

ACTH measurement (EDTA plasma):

Primary Morbus Addison: increased. Secondary: decreased

Electrolytes:

Hyponatremia (<135 mmol/l), hyperkalemia (>5.5 mmol/l), therefore: Na/K-ratio <27:1 (most important parameter)

Blood count:

Normocytic normochromic anaemia, leucocytes in normal range with neutropenia, lymphocytosis and eosinophilia

Clinical chemistry:

Azotemia, increased phosphate, hypoalbuminemia, hypercalcemia, urine specific gravity of 1.015 to 1.030

Basal cortisol:

If the basal cortisol level is > 12 ng/ml, Morbus Addison is highly unlikely.

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