MEDICAL TREATMENT OF CANINE PITUITARY-DEPENDENT HYPERADRENOCORTICISM (CUSHING’S DISEASE)

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Hyperadrenocorticism is a relatively common endocrine disorder of middle- to old-aged dogs. Pituitary-dependent hyperadrenocorticism accounts for 85% to 90% of cases, and adrenocortical neoplasia is responsible for the remainder. The choice of treatment for a given dog with hyperadrenocorticism depends on several factors, including cause, severity of disease, presence of malignancy, available treatment options, and clinician and client preferences. It is important to remember, however, that not all dogs with hyperadrenocorticism, especially dogs with pituitary-dependent hyperadrenocorticism, need immediate treatment. A recent survey of internists and dermatologists revealed that more than 50% of board-certified specialists would not treat a dog that has no signs or only minimal clinical signs despite abnormal biochemical or endocrine tests consistent with pituitary-dependent hyperadrenocorticism. Treatment of hyperadrenocorticism is not always a benign procedure and should not be initiated unless the dog shows unambiguous clinical signs of the disease.

There are three treatments commonly used in the management of pituitary-dependent Cushing’s disease in dogs: mitotane (o,p’-DDD [Lysodren]), ketoconazole (Nizoral), and t-deprenyl (selegiline hydrochloride [Anipryl]). These medications are associated with the potential

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for different side effects and expense, but all can produce satisfactory results in dogs with pituitary-dependent Cushing’s disease.

MITOTANE

Mitotane is the drug most commonly used for the treatment of hyperadrenocorticism in dogs. Management of canine pituitary-dependent hyperadrenocorticism with mitotane was first described over 20 years ago. Mitotane is an adrenocorticolytic agent with a direct cytotoxic effect on the adrenal cortex, resulting in selective progressive necrosis and atrophy.

The systemic availability of mitotane administered as intact tablets to fasting dogs is poor. One study demonstrated that the availability of mitotane was improved with emulsion of the drug in oil, better with intact tablets given in food, and best with ground tablets in oil given in food. The reason for these findings can be explained by the fact that mitotane is a fat-soluble drug. Furthermore, Watson et al showed that the availability of intact tablets given with food was greater in dogs with pituitary-dependent hyperadrenocorticism than in normal dogs, presumably because of enhanced intestinal absorption of the drug. Poor absorption of mitotane may contribute to the apparent “resistance” to the effects of the drug seen in some dogs with hyperadrenocorticism. On the basis of these studies, it is recommended that mitotane be administered with meals. Crushing the tablets cannot be recommended, however, because of the potential carcinogenic and mutagenic effects of the drug and the risk of human exposure (see product information for mitotane). Another option is to obtain mitotane as a customized formulation, a service provided by several veterinary pharmacies. Inasmuch as intestinal fat absorption is greater than normal in dogs with hyperadrenocorticism and diminishes after treatment with mitotane, availability of mitotane might decrease as treatment proceeds, even if the drug is administered with food.

Mitotane is by far the most commonly used drug for the treatment of dogs with pituitary-dependent hyperadrenocorticism. Although variations of the protocol originally suggested by Schechter et al in 1973 have been reported, most clinicians still use an initial loading dosage of mitotane followed by a weekly maintenance dosage of the drug.

Initial Induction or Loading Dosage

The induction dosage of mitotane is 30 to 50 mg/kg/d administered for 10 days or until clinical signs suggestive of hypoadrenocorticism develop. An induction dosage of greater than 50 mg/kg/d is rarely required and causes a higher incidence of hypoadrenocorticism. In moderate- to large-sized dogs, dividing the daily dosage into two equal doses may be better; however, because mitotane is available only as a scored 500-mg tablet, it may be difficult to provide a dosage in small and toy breeds of dogs.

Concurrent glucocorticoid supplementation (prednisolone 0.15–0.25 mg/kg/day, or 0.2 mg/d per dog) can be used to manage hyperadrenocorticism with serum cortisol concentrations in the normal range. During this initial period, either 1-mg prednisone tablets containing 1 mg/mL of prednisolone or 10-mg tablets containing 1 mg/mL of prednisolone should be used. Intermittently administer the small maintenance dose of mitotane to the dog during the induction period is the initial strategy, and when an adequate total induction dosage is administered, or even if overdosage of glucocorticoid deficiency may manifest itself. Inasmuch as the corticosteroid level is a surrogate marker for the development and immediate veterinary hospitalization.

Clinical signs that owners should immediately report to their veterinarian, and water intake. Awareness of the need to stop the drug is stopped before the induction period and when monitoring by the owner has been initiated. Inasmuch as the corticosteroid level is a surrogate marker for the development and immediate veterinary hospitalization.

At home, the most reliable means of evaluating the effects of mitotane induction is to observe the appetite. A common early sign of mitotane induction is a decrease in appetite, which almost always occurs. All clinical signs (e.g., vomiting, weight loss) should be observed by the owner. A decrease in appetite should be observed by the owner. If the dog’s appetite diminishes (or not at all), the owner should report it to the veterinarian.

In addition to providing an improved quality of life for the dog at the time of feeding, mitotane improves appetite because it is a fat-soluble drug.

After completion of mitotane induction, the veterinarian should again see the dog and perform a complete physical examination to determine whether the dog has responded clinically or not, the effects of the drug on the dog should be determined.
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The only used for the treatment of canines was first described over 20 cytoxic agent with a direct cytotoxic in selective progressive adrenocorticism. The administered as intact tablets demonstrated that the availability of 10-150 mg/kg/d in small, can be explained by the fact that more, Watson et al. showed that with food was greater in dogs corticosteroid than in normal dogs, enteric absorption of the drug. 20 is known to the apparent "resistance" dogs with hyperadrenocorticism. Recommended that mitotane be tablets cannot be recommended, mutagenic and carcinogenic effects of exposure (see product information Mitotane as a customized general veterinary pharmacies. Not greater than normal in dogs with after treatment with mitotane, 20 as treatment proceeds, even if the only used drug for the treatment of hyperadrenocorticism. Although varied by Schechter et al. in 1973 use an initial loading dosage of the daily dosage of the drug. 6, 8, 10, 12, 14

30 to 50 mg/kg/d administered as a scored 500-mg tablet, it may be impossible to divide the daily dosage in small and toy breeds of dogs.

Concurrent glucocorticoid supplementation with prednisone or prednisolone (0.15-0.25 mg/kg/d up to a maximal daily dosage of 5 mg/d per dog) can be used to mitigate the adverse effects associated with serum cortisol concentrations falling rapidly into the normal or subnormal range during this initial treatment period. 5, 10, 12, 14 In small dogs, either 1-mg prednisone tablets or an oral liquid preparation containing 1 mg/mL of prednisolone (PediaPrep) should be used to accurately administer the small maintenance dosage needed. The major disadvantage of providing a low maintenance dosage of glucocorticoid during the induction period is that it may be possible to know if and when an adequate total induction dosage of mitotane has been administered, or even if overdosage has occurred, because clinical signs of glucocorticoid deficiency may not develop. 2 If the veterinarian elects not to provide glucocorticoid supplementation during the induction period, it is imperative that the owners are supplied with prednisone or prednisolone in case signs of life-threatening hyperadrenocorticism develop and immediate veterinary care is not available.

Clinical signs that owners should monitor before and during the administration of mitotane to their dog include the dog's attitude, appetite, and water intake. Awareness of these signs helps to determine if the drug should be stopped before completion of the 10-day induction period and when monitoring by the corticotropin stimulation test is needed. Inasmuch as the corticotropin stimulation test is the best means to determine the ability of the adrenal cortex to secrete cortisol (and therefore judge the thinning of the cortex), this is the test of choice for monitoring the effects of mitotane. 5, 10, 12, 14

At home, the most reliable means that the owner has of monitoring the effects of mitotane induction is careful monitoring of the dog's appetite. 6 A common early sign of adequate control is a decrease in appetite, which almost always occurs before development of any other clinical signs (e.g., vomiting, weakness, complete anorexia). The dog's appetite should be observed by the owner before administration of the daily dosage. If the dog rapidly consumes the meal, the owner should administer the dose of mitotane immediately after the dog finishes the food. If the dog's appetite diminishes (the food is consumed either slowly or not at all), the owner should not administer any more mitotane to the dog, at least until he or she consults with the veterinarian. In addition to providing an important monitoring tool, administering mitotane at the time of feeding enhances its gastrointestinal absorption because it is a fat-soluble drug. 22

After completion of mitotane induction (i.e., when clinical signs suggestive of adequate control develop or after a maximum of 10 days), the veterinarian should again see the dog, collect a thorough history, and perform a complete physical examination. Whether the dog has responded clinically or not, the efficacy of induction should always be determined by performing a corticotropin stimulation test. 5, 10, 12, 14 If
glucocorticoid was administered during mitotane induction, it should not be given on the morning of corticotropin stimulation testing, because some glucocorticoids (e.g., prednisone, prednisolone) can cross-react in the cortisol assay to falsely elevate the serum cortisol concentration. Because the maintenance dosage of glucocorticoid used in this protocol is low (0.15–0.25 mg/kg/d), it is not necessary to withdraw therapy for up to 2 days as has been suggested by others. Once the corticotropin stimulation test has been completed, that day’s glucocorticoid dose can be given if needed.

The goal of treatment with mitotane is to achieve a corticotropin stimulation test result that suggests relative but not complete hypoadrenocorticism. In other words, the basal (resting) cortisol should be lowered into the reference range (1–4 µg/dL or 25–125 nmol/L) with little to no rise in cortisol concentration after corticotropin stimulation (postcorticotropin cortisol concentration should also be lowered into the reference range for basal cortisol, i.e., <4 µg/dL or <125 nmol/L).

In most dogs with pituitary-dependent hyperadrenocorticism, initial daily mitotane treatment succeeds in decreasing basal and postcorticotropin serum cortisol concentrations into the desired range. In some dogs, however, the corticotropin-stimulated serum cortisol concentration falls to subnormal values (<1 µg/dL or <25 nmol/L) after the initial treatment period, indicating near-total adrenocortical destruction. In this situation, mitotane should be stopped and glucocorticoid should be provided until the corticotropin-stimulated serum cortisol concentration rises to within the reference range for basal cortisol (1–4 µg/dL or 25–125 nmol/L). After overtreatment with mitotane, the low serum cortisol concentration typically increases spontaneously into the desired range within 2 to 6 weeks; however, in a few dogs, cortisol remains low for up to 18 months without further mitotane.

Conversely, about 10% to 15% of dogs still respond to exogenous corticotropin with the serum cortisol concentration rising to above the desired range (>4 µg/dL or >125 nmol/L) after initial daily mitotane treatment. In these dogs, daily mitotane administration should be continued and the corticotropin stimulation test should be repeated at weekly intervals until adverse clinical signs develop or the circulating cortisol concentration falls into the desired range.

Dogs have individual sensitivity to mitotane during the induction period, and the length of daily treatment needed to adequately reduce adrenal reserve can range from 5 days to 2 months. No reliable method has been determined for predicting either the duration of treatment necessary or the amount of mitotane necessary to destroy enough adrenal tissue for a detectable response.

**Maintenance Dosage**

Once adrenal reserve has been appropriately reduced as determined by corticotropin stimulation test results, mitotane should be continued at a maintenance dosage of 0.15–0.25 mg/kg/d for 2 days, then for a total of three divided doses. It is practical to attempt to discontinue maintenance therapy if the postcorticotropin serum cortisol concentration has returned to or remains below the reference range. During periods of stress, glucocorticoid supplementation may be necessary.

About half of the dogs with pituitary-dependent hyperadrenocorticism respond to mitotane by recurrence of clinical signs, and therefore, corticotropin-stimulated cortisol concentrations remain elevated. Prompt corticotropin stimulation testing should be performed every 3 to 6 months to determine whether mitotane treatment is still indicated. If the dog does not respond adequately to mitotane therapy, glucocorticoid supplementation can be considered.

Side effects are relatively rare. Mitotane administration, even in high doses (e.g., 0.2–0.5 mg/kg), is generally well tolerated, and the most common side effects are anorexia, vomiting, diarrhea, dehydration, and lethargy. Dogs can develop one or more side effects. Most dogs show a complete resolution of side effects within 2 to 3 weeks; persisting side effects may signify another medical problem.

Likewise, adverse reactions to mitotane therapy, most commonly vomiting, diarrhea, and dehydration, occur during therapy or during relapses. The development of side effects necessitating corticosteroid supplementation in the maintenance period usually signifies another medical problem.
mitotane induction, it should be borne in mind that mitotane can cross-react in some serological tests. Serum cortisol concentration should be measured in the mitotane-treated animal. In mitotane-treated dogs with basal cortisol concentrations of 12-25 μg/dl or 25-125 nmol/L with a rise in cortisol stimulation after corticotropin stimulation should also be lowered into the range of 12-25 μg/dl or <125 nmol/L.

In hyperadrenocorticism, initial treatment involves decreasing basal and postcorticotropin-stimulated cortisol concentrations. In some dogs, serum cortisol concentration below 25 nmol/L after the initial mitotane administration. In this case, mitotane should be continued until serum cortisol concentration is within the desired range. If the dog continues to respond to exogenous corticotropin stimulation, the dose of mitotane should be reduced gradually. If the dog is not responding to mitotane, the dose should be increased to a level that is likely to be effective. If mitotane is discontinued, mitotane should be continued at a maintenance dosage of approximately 50 mg/kg/wk given in two to three divided doses. 

In small or toy breed dogs, it may not be practical to attempt to divide the weekly dosage. Daily glucocorticoid supplementation is rarely necessary during maintenance mitotane treatment. During periods of stress or illness, however, appropriate dosages of glucocorticoids may be necessary. Despite initial control of hyperadrenocorticism with mitotane, relapse commonly occurs during long-term treatment.

About half of the dogs treated with initial loading and maintenance dosages of mitotane relapse within 12 months of treatment as evidenced by recurrence of clinical signs and higher than desired basal and corticotropin-stimulated cortisol concentrations. To ensure continued control and prevent serious relapse during mitotane treatment, corticotropin stimulation testing should be repeated after 3 and 6 months of maintenance treatment and every 6 months thereafter. If basal and postcorticotropin cortisol concentrations exceed desired ranges (>4 μg/dL or >125 nmol/L), the dog should be reloaded (i.e., the mitotane dosage should be increased to 30 to 50 mg/kg daily for 5 to 7 days or longer if needed). Once circulating cortisol concentrations have again been lowered into the desired range, the weekly maintenance dosage can be increased by approximately 50% to help prevent further relapse. Because of multiple relapses, some dogs eventually require extremely high maintenance mitotane dosages to control hyperadrenocorticism.

Side effects are relatively common and should be anticipated during mitotane administration, especially during induction of mitotane. The adverse effects most commonly observed include lethargy, weakness, anorexia, vomiting, diarrhea, and ataxia. Up to a quarter of dogs can develop one or more of these problems during the period of initial mitotane administration, but they are generally mild in most dogs. These effects develop as the serum cortisol concentration falls rapidly to normal or subnormal (glucocorticoid with drawal) and typically resolve rapidly when mitotane is discontinued and glucocorticoid supplementation is increased.

When side effects develop during the induction period, mitotane should be discontinued and a glucocorticoid should be administered (e.g., 0.2-0.5 mg/kg of prednisone) until the dog can be examined and corticotropin stimulation testing can be performed to evaluate adrenal reserve. Most dogs show a clinical response to the glucocorticoid dosage within 2 to 3 hours; persistence of problems for longer than a few hours after administering or increasing the glucocorticoid dosage usually signifies another medical problem.

Likewise, adverse reactions may occur in dogs during maintenance mitotane therapy, most commonly shortly after beginning maintenance therapy or during relapses when daily therapy is reinstituted. Again, the development of side effects is associated with a subnormal circulating cortisol concentration in most dogs. If side effects occur during the maintenance period, mitotane should be discontinued and glucocorticoid supplementation should be provided. Should adverse signs persist.

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for longer than a few hours after administration of a glucocorticoid, the
dog should be evaluated as soon as possible to exclude other disorders,
including mineralocorticoid insufficiency. In most dogs, it is necessary
to resume maintenance mitotane in 2 to 8 weeks as determined by
corticotropin stimulation test results and clinical signs.9, 10, 12, 14

In a few dogs treated with mitotane, the same clinical signs may
result from direct drug intolerance rather than absolute or relative hypo-
adrenocorticism. In such dogs, the serum cortisol concentration is not
low, and no improvement in adverse clinical signs occurs when glucor-
tocoid supplementation is given. Dividing the daily or weekly dosage of
mitotane into several smaller doses may lessen or eliminate the adverse
reactions in these dogs.

The most serious adverse effect associated with mitotane adminis-
tration is the development of total or near-total adrenocortical destruc-
tion with concomitant glucocorticoid and mineralocorticoid deficiency
and hyperkalemia and hyponatremia (Addison’s disease).9, 10, 12, 14, 23
Iatrogenic Addison’s disease secondary to mitotane is relatively rare, develop-
ing in less than 5% of dogs.9 The complication may develop any
time during maintenance treatment but is likely to develop during the
first year of mitotane administration.9 Unfortunately, predicting which
dogs are likely to develop Addison’s disease does not seem possible. In
one study, no difference was found in the maintenance dosages of
mitotane between those dogs that developed complete adrenocortical
insufficiency and those that did not.9

In general, Addison’s disease should be suspected if a dog develops
side effects during mitotane administration and does not promptly re-
respond to glucocorticoid supplementation. Iatrogenic Addison’s disease
is confirmed in these dogs by corticotropin stimulation testing (i.e.,
undetectable serum cortisol concentration before and after corticotropin
administration) and serum electrolyte determination (i.e., hyperkalemia
and hyponatremia).9, 10, 12, 14, 23

If Addison’s disease does develop, mitotane should be discontinued,
and appropriate glucocorticoid and mineralocorticoid replacement
therapy should be instituted immediately. Of the dogs that develop complete
iatrogenic adrenal insufficiency, all can be expected to require mineralo-
corticoid and glucocorticoid replacement therapy for the remainder of
their lives.9 Further mitotane administration in the future is usually not
necessary.

LEVODEPRENYL

Unlike Cushing’s disease in human beings, which is usually associ-
ated with a microadenoma in the anterior lobe (pars distalis), Cushing’s
disease in dogs can be caused by adenoma or hyperplasia of cells in
either the pars distalis or pars intermedia.16, 17 Approximately 70% of
dogs with Cushing’s disease have a pituitary adenoma that arises from
the pars distalis, whereas 30% have a tumor that arises from the pars
intermedia. This hetero-

geneity in the pituitary of dogs was more than one underly-

An increasing body of evidence suggests that the neurontransmitter dop-
aminergic neurons of the pars distalis and pars intermedia; consequently, it is
likely that mitotane could affect dopamine (a dopaminergic neurotransmitter) and
shows a hormonal effects associated with the

1-Deprenyl (selegiline), an inhibitor of monoamine oxidase (MAO), has
several mechanisms.4 The mechanism of action of these agents may vary, as
animal studies suggest. For example, levodopa (a dopaminergic neurotransmitter)
markedly improves severity and level of activity, which has been
amphotamine concentration.

The drug was generally well tolerated in dogs and often had a good response to 1-depen-

Dosage of Levodoprenyl

Treatment is initiated at 2 mg/kg/day and increased by 2 mg/kg/day at the end of each week.

5. Treatment is initiated at 2 mg/kg/day and increased by 2 mg/kg/day at the end of each week.

6. Treatment is initiated at 2 mg/kg/day and increased by 2 mg/kg/day at the end of each week.
intermedia. This heterogeneous nature of the pathologic changes found in the pituitary of dogs with Cushing’s disease could indicate that there is more than one underlying cause for this disorder.\textsuperscript{16, 17}

An increasing body of evidence indicates that a central disturbance of the neurotransmitter dopamine may play a role in the pathogenesis of Cushing’s disease in dogs.\textsuperscript{4, 13, 15, 17} In dogs, dopamine primarily seems to inhibit the secretion of corticotropin peptides from the pars intermedia, but it may also affect corticotropin release from the pars distalis.\textsuperscript{4} Administration of dopaminergic antagonists to dogs results in increases of pars distalis and pars intermedia pro-opiomelanocortin peptide secretion\textsuperscript{1}; consequently, it is conceivable that a central disturbance in this neurotransmitter could affect both pituitary lobes. In studies of bromocriptine (a dopaminergic agonist) in dogs with Cushing’s disease, a few dogs showed a hormonal and clinical response to treatment, but adverse effects associated with the drug (e.g., vomiting, anorexia) precluded its routine clinical use.\textsuperscript{13, 19}

\textbf{1-Deprenyl} (selegiline hydrochloride) is a selective and irreversible inhibitor of monoamine oxidase type B that helps to restore the central dopamine concentration and facilitates dopaminergic transmission by several mechanisms.\textsuperscript{4} The drug’s effect is similar to that of the dopaminergic agonists such as bromocriptine. In studies sponsored by Deprenyl Animal Health, investigators treated 90 dogs with Cushing’s disease for up to 6 months and concluded that 83\% of the dogs had partial to complete clinical improvement with negligible side effects.\textsuperscript{18} However, in the only in-depth independent investigation of 1-deprenyl for treatment of pituitary-dependent hyperadrenocorticism in dogs, investigators found that the drug was much less effective.\textsuperscript{18} Of the 10 dogs with pituitary-dependent hyperadrenocorticism studied, only 2 (20\%) showed a good response to 1-deprenyl, whereas other dogs showed improvement in some signs. Many of these latter dogs showed an increase in level of activity, which was probably related to a high circulating amphetamine concentration resulting from the metabolism of 1-deprenyl.\textsuperscript{4, 18}

The drug was generally well tolerated by all 10 dogs with hyperadrenocorticism studied, with no serious side effects. In addition, no increase in the size of the pituitary mass was found in the 2 dogs that had a good response over the 6-month course of the study, suggesting that the drug may have a suppressive effect on the growth of the pituitary mass in these dogs. This is similar to the effect that dopamine agonists can have on some pituitary tumors (i.e., prolactinomas) in human patients.

\textbf{Dosage of Levodeprenyl}

Treatment is initiated at a dosage of 1 mg/kg daily, preferably administered in the morning. If no response is observed after 2 months of treatment, the dosage can be increased to 2 mg/kg/d for an additional
month. If this dosage also proves ineffective, alternative treatment is necessary. If effective, daily treatment is generally continued for the remainder of the dog’s life. Inasmuch as t-deprenyl is neither adrenolytic nor an inhibitor of steroidogenesis, corticotropin stimulation testing and routine measurement of serum electrolytes are not necessary. Response to treatment is judged primarily by resolution of clinical signs. If a good response is observed, normalization of results of low-dose suppression tests and urinary cortisol:creatinine ratios should also be seen.

T-deprenyl seems to be a safe treatment alternative in most dogs with hyperadrenocorticism. Nevertheless, t-deprenyl is not currently recommended for treatment of pituitary-dependent hyperadrenocorticism in dogs with concurrent diabetes mellitus, pancreatitis, heart failure, renal disease, or other severe illness. The drug should not be administered concurrently with other monoamine oxidase inhibitors, opioids, or tricyclic antidepressants such as fluoxetine, because severe adverse drug interactions have been reported in human beings.

Recommendations Concerning the Use of Levodeprenyl in Dogs with Pituitary-Dependent Hyperadrenocorticism

Is a 20% success rate unacceptable? It certainly may be if the dog has severe Cushing’s disease or if the disease is progressing rapidly. Conversely, in dogs with milder disease that is progressing slowly, the drug’s safety may justify its use. Once one accepts that the drug is useful in a certain percentage of dogs and that one should wait only 2 to 3 months before switching to another treatment modality such as mitotane if the response to t-deprenyl is poor, the lower response rate may not really be so bad. In addition, even in dogs with more advanced disease, it may not be wise for a veterinarian inexperienced with the use of mitotane to administer this drug, whereas the same veterinarian may feel more comfortable using t-deprenyl because of its association with fewer side effects, none of which are life threatening. It is not known at present whether use of t-deprenyl would be beneficial in a dog testing positive for Cushing’s disease that is showing no clinical signs.

KETOCONAZOLE

Ketoconazole is an imidazole antifungal drug that lowers the circulating cortisol concentration by enzymatic inhibition of steroid biosynthesis. The drug has minimal effect on mineralocorticoid production. Ketoconazole effectively controls hyperadrenocorticism in some dogs, but, unfortunately, the drug is not efficacious in many dogs with the disease. In this author’s experience, one third to one half of dogs fail to adequately respond to treatment.

Dosage

The initial recommendation is 25 mg/kg daily for 14 days. Alterna-
daily for the first 7 days before increasing the dosage to 10 mg/kg.

The efficacy of the initial treatment is assessed by a corticotropin stimulation test. If the basal corticosterone concentrations must be lowered in the serum cortisol concentration is increased to 15 mg/kg, and the test is repeated in 14 days. If the test is still positive, 2 mg/kg of metyrapone, which inhibits ACTH production, is added to the treatment regimen, and the test is repeated in 14 days.

Adverse effects seen in humans are uncommon and include nausea, vomiting, and diarrhea. In dogs, the most common adverse signs associated with glucocorticoid supplementation usually are weight gain, decreased appetite, and hyperglycemia.

OVERVIEW OF TREATMENT OPTIONS FOR PITUITARY-DEPENDENT HYPERCORTISOLISM

Of the three treatment options available for pituitary-dependent Cushing’s disease in dogs, ketoconazole is effective in controlling the clinical signs of hyperadrenocorticism associated with hyperadrenocorticism, but it also produces many adverse clinical signs that are usually debilitating. Ketotifen, an antihistaminic agent, is an effective second line of treatment with fewer side effects than mitotane. The drug is not very effective and is only effective in less than 50% of dogs when used alone. Ketotifen is a second line of treatment for only severe cases of hyperadrenocorticism.

Ketoconazole is an effective treatment for hyperadrenocorticism but is only partially effective due to its side effects and its inability to control the clinical signs. As a result, it may be necessary to combine it with other medications to reduce its side effects and control clinical signs. The most common side effects associated with ketoconazole treatment are nausea, vomiting, and diarrhea. These side effects are usually mild and can be controlled with the use of other medications. The most common side effects associated with mitotane treatment are weight gain, decreased appetite, and hyperglycemia. These side effects are usually mild and can be controlled with the use of other medications. The most common side effects associated with metyrapone treatment are weight gain, decreased appetite, and hyperglycemia. These side effects are usually mild and can be controlled with the use of other medications.

References

ive, alternative treatment is generally continued for the 1-deprenyl is not currently preferred by dogs with dependent hyperadrenocorticosis, pancreatitis, heart failure, or because severe adverse drug reactions. Tents.

Dosage

The initial recommended dosage of ketoconazole is 10 mg/kg twice daily for 14 days. Alternatively, treatment is initiated at 5 mg/kg twice daily for the first 7 days to assess drug tolerance and is then increased to 10 mg/kg.

The efficacy of the initial 14-day course of treatment is determined by a corticotropin stimulation test. To ensure adequate control of hyperadrenocorticosis, the basal and postcorticotropin serum cortisol concentrations must be lowered into the basal reference range as for mitotane. If the serum cortisol concentrations remain above this range, the dosage is increased to 15 mg/kg twice daily, and a corticotropin response test is repeated in 14 days. Dosages of up to 20 mg/kg twice daily are occasionally necessary.

Adverse effects seen in dogs receiving ketoconazole are relatively uncommon and include vomiting, anorexia, diarrhea, and transiently high liver enzyme activity. Such drug intolerance may, however, necessitate permanent discontinuation of ketoconazole. In addition, clinical signs associated with glucocorticoid deficiency can occur during ketoconazole administration. Discontinuation of ketoconazole and glucocorticoid supplementation usually results in rapid resolution of signs.

OVERVIEW OF TREATMENT OPTIONS FOR PITUITARY-DEPENDENT HYPERADRENOCORTICISM

Of the three treatments used in the management of pituitary-dependent Cushing’s disease in dogs, mitotane remains the drug that is most effective in controlling the clinical signs of the disease. Virtually all dogs with hyperadrenocorticosis respond to mitotane, but the incidence of adverse clinical signs is the highest with this drug.

Ketoconazole, an antifungal drug that can lower circulating cortisol concentrations by enzymatic inhibition of steroid biosynthesis, is safer than mitotane. The drug must be administered twice a day, however, and is only effective in lowering serum cortisol concentration in one third to one half of dogs with pituitary-dependent hyperadrenocorticism. Finally, 1-deprenyl is by far the safest of the three drugs used to treat this disease but is only effective in 20% of dogs with hyperadrenocorticism. As a result, 1-deprenyl should be reserved for dogs with mild to moderate hyperadrenocorticism in which the drug’s safety may justify its use. If no response is observed after 2 to 3 months of 1-deprenyl treatment, alternative treatment with mitotane should be instituted.

References


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HISTORY OF HYPOPHYSECTOMY

The history of hypophysectomy is strongly interrelated. Before 1886, hypophysectomies were performed to relieve the symptoms of pituitary hyperplasia. Hypophyselomies arrived at the conclusion that hypophysectomy was the treatment of choice for pituitary disease. In 1886, Victor Horsley published a report on the treatment of pituitary disease in dogs, using a lateral temporal craniotomy and 6 months, respectively, with similar results. In 1888, Paulsen reviewed the results of hypophysectomy and concluded that it was necessary for life. In 1898, none of 22 dogs survived long-term hypophysectomy.

Harvey Cushing (1869–1939) popularized the field of brain surgery in the first half of the 20th century. He is credited with the same bilateral temporal lobectomy that has been used in the treatment of intractable seizures in humans. He also performed the first successful hypophysectomy in a human in 1912, as shown by microsurgical studies of the hypothalamus of animals. In 1912, Aschauer recommended the use of the temporal lobe hypophysectomy for the treatment of intractable seizures in humans. In 1917, he reported the first successful hypophysectomy in a human patient. He also reported the first successful hypophysectomy in a human patient. He also reported the first successful hypophysectomy in a human patient.