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Mitotane & Trilostane

Pituitary-dependent hyperadrenocorticism (PDH) is a common canine endocrinopathy.

Affected dogs have a functional pituitary tumor that secretes excessive amounts of adrenocorticotropic hormone (ACTH); this leads to bilateral adrenocortical enlargement and stimulation of adrenal hormone production, especially cortisol. In most dogs, clinical signs of PDH are related to hypercortisolemia.

Definitive treatment of PDH requires hypophysectomy or radiation therapy, but many owners choose pharmacologic therapy. This therapy reduces adrenal hyperfunction and ameliorates clinical signs of hypercortisolemia. Mitotane and trilostane are the most common drugs used to treat canine PDH.

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ACTH = adrenocorticotropic hormone;
PDH = pituitary-dependent hyperadrenocorticism

MITOTANE

INDICATIONS

Mitotane is a pharmacologic adrenocorticolytic that primarily targets the zona fasciculata, with lesser action on the zona reticularis. While it is not approved in dogs, it is indicated for several canine diseases:

- PDH (primary veterinary indication)
- Non–pituitary-dependent conditions causing primary adrenal hyperfunction, such as nodular adrenal hyperplasia
- Adjunctive therapy for functional adrenal neoplasia (may alleviate clinical signs prior to definitive therapy, such as adrenalectomy)
- Palliative measure for dogs with inoperable tumors or metastasis, or when definitive therapy is declined.

CONTRAINDICATIONS & DRUG INTERACTIONS

Mitotane has a narrow therapeutic index due to its toxicity, which necessitates close attention to dosing and careful patient monitoring. It is important to confirm diagnosis of hyperadrenocorticism prior to instituting mitotane therapy; empiric use of mitotane is not recommended.

ADVANTAGES

In the majority of cases, mitotane produces excellent control of clinical signs associated with canine PDH.[1] While mitotane is a highly efficacious adrenocorticolytic, treatment success is facilitated by extensive clinical experience. Detailed guidelines for troubleshooting therapy are available[1] and many veterinarians feel comfortable making adjustments to therapy if the initial therapeutic response is sluggish or less than optimal.

DISADVANTAGES

Adrenolytic therapy is not definitive therapy for PDH. Furthermore, although mitotane has no direct effect on abnormal ACTH-producing pituitary cells, stimulation of tumor growth following reduction in the circulating cortisol level and interruption of cortisol feedback is an undesirable, indirect effect that occurs in about 20% of treated dogs.[1]

Dosing. Mitotane is supplied in 500-mg tablets that must be fractioned for use in most dogs. Some pharmacies compound alternative formulations, but caution is warranted as efficacy of compounded formulations has not been studied.

Although guidelines for mitotane therapy are well established, precise dosing is challenging. Some dogs may not tolerate the loading dose or the loading period may be difficult to predict. Thus, careful monitoring is needed during early stages of therapy. Furthermore, periodic adjustments should be anticipated since as many as 35% of dogs receiving mitotane will experience a relapse of clinical signs.[1]

Once the maintenance dose is established, most clinicians administer the weekly dose of mitotane as divided doses on several days. A common approach is to give half the weekly dose 3 days apart (eg, half on Monday, the other half Thursday).

Side Effects. Mitotane can produce significant side effects, necessitating temporary interruption of therapy. Adverse reactions, representing drug intolerance, are common and include gastrointestinal disturbances, such as inappetence, vomiting, and diarrhea.[2] Unfortunately, mitotane overdose may present with similar side effects due to drug-induced adrenocortical insufficiency. The difficulty in identifying overtreated dogs based on clinical signs alone underscores the importance of regular assessment of adrenal function.

Special Handling. Veterinarians and owners should exercise appropriate cautions when administering mitotane, including routine use of latex gloves when handling the drug. The risk for inadvertent human exposure may be increased when tablets are broken apart. Although the reproductive, developmental, and carcinogenic effects of mitotane are not well studied, pregnant and nursing women should be advised to avoid exposure.

MONITORING

During both loading and maintenance phases, the ACTH stimulation test is preferred for monitoring adrenal function in dogs receiving mitotane. During drug loading, adrenal function should be assessed as soon as clinical signs of hypercortisolemia begin to abate (eg, urine volume reduced) or the dog develops inappetence. In order to avoid possible side effects from drug overdose, adrenal function should be assessed no later than 1 week after the loading phase is begun. Typically, serum biochemistry parameters, including serum electrolytes, are also assessed at this time.

Once the maintenance dose is established, ACTH stimulation and electrolyte assessment are performed every 3 to 4 months as long as the dog is clinically stable. In less stable patients, ACTH stimulation testing is indicated anytime the dog exhibits signs of mitotane overdose, if clinical signs of hyperadrenocorticism appear, and following any adjustment in the mitotane dose. Typically the ACTH stimulation test is performed 2 to 4 weeks after a dose change, with the longer period selected when slight dose changes are recommended.

Regardless of the treatment phase, the target baseline cortisol level should be within the laboratory's normal range (usually 1–5 mcg/dL), with very little change in the post-stimulation cortisol value.

ECONOMIC IMPACT

Mitotane is expensive and most dogs with PDH require lifelong treatment. At a maintenance dose of 50 mg/kg/week, cost for a 15-kg dog ranges from $9 to $18/week or approximately $500 to $1000/year (estimates based on quoted prices from several veterinary pharmacies). In addition, owners must anticipate recurring costs associated with monitoring therapy (ie, veterinary visits and ACTH stimulation testing).

TRILOSTANE

INDICATIONS

Trilostane selectively inhibits 3-ß-hydroxysteroid dehydrogenase (3ß-HSD), an enzyme involved in adrenal synthesis of cortisol and other hormones, in the zona fasiculata. This causes greater reduction of cortisol synthesis than aldosterone and sex hormone synthesis.[3] Trilostane is indicated for treatment of canine PDH and functional adrenocortical neoplasia.

CONTRAINDICATIONS & DRUG INTERACTIONS

Trilostane is contraindicated in dogs with primary hepatic or renal disease, those with hypersensitivity to the drug, and in pregnant bitches. Trilostane and ACE inhibitors should be used with caution because trilostane potentiates the effects of ACE inhibitors. Concurrent use of trilostane and spironolactone is contraindicated. Empiric administration of trilostane is not recommended and its use should be restricted to dogs with confirmed hyperadrenocorticism.

ADVANTAGES

Trilostane is approved for treatment of canine PDH in the U.S. and many European countries. Capsule sizes (120, 60, 30, and 10 mg)* are formulated to facilitate typical canine dosing regimens. Alternative trilostane formulations are available from compounding pharmacies, but the efficacy of these formulations has not been evaluated.

Experience from Europe suggests trilostane is an effective and safe treatment for canine PDH. It reportedly has a lower incidence of side effects compared with mitotane.[3] A major advantage of trilostane is that 3ß-HSD suppression is reversible, which permits rapid recovery of adrenal function in the event of overdose.

DISADVANTAGES

As mentioned earlier, the major disadvantage of adrenolytic therapy is that it is not definitive therapy for PDH.

Dosing. Unlike mitotane, trilostane is administered on a daily schedule. The drug is labeled for once daily dosing but published studies have supported twice daily administration. A recent study reported that twice daily administration permitted a reduction in the total daily dose in dogs with PDH, which may have a large impact on total drug costs over time.[4]

Side Effects. Commonly reported adverse reactions include inappetence, vomiting, lethargy, diarrhea, and weakness. Rarely reported, but potentially fatal, reactions include hemorrhagic diarrhea, collapse, hypoadrenocortical crisis, and adrenal necrosis.[2,3]

Special Handling. Specific recommendations for handling trilostane should be reviewed with owners to reduce the risk of inadvertent human exposure. Fortunately, handling and administration of trilostane carries less risk compared to mitotane; however, pregnant or nursing women should avoid handling it. Trilostane capsules should not be broken apart prior to administration.

MONITORING

Recommendations for monitoring adrenal function in dogs receiving trilostane vary from study to study and the optimal monitoring protocol remains to be clarified. Pharmacokinetic data indicates that ACTH stimulation testing should be performed within 6 hours following drug administration, but recommendations range from 2 to 6 hours.[3] The target post-ACTH stimulation cortisol level and optimal adrenal function parameters used in published studies have been inconsistent.[3] Reevaluation, including an ACTH stimulation test and serum electrolytes, should be done 7 to 14 days after beginning therapy and repeated at 30 and 90 days (sooner if signs of hypoadrenocorticism appear).

ECONOMIC IMPACT

Trilostane therapy for PDH is life long; owners should anticipate significant expense over time. Trilostane and mitotane costs appear comparable. For example, drug costs for a 15-kg dog receiving 60 mg/day of trilostane (4 mg/kg/day) will be roughly $25/week or $1300/year (estimated costs at university veterinary pharmacy). Recurring costs for veterinary visits and adrenal function testing for dogs receiving trilostane are comparable to those for dogs receiving mitotane.

See Aids & Resources, back page, for references, contacts, and appendices.

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Take Note

- Mitotane and trilostane are the most common drugs used to treat canine PDH.
- Therapy should be instituted only when diagnosis is confirmed.
- Neither drug provides definitive therapy for PDH.
- Careful monitoring is required in the early stages of therapy and on a regular basis thereafter.
- Mitotane is administered weekly (dose commonly split between 2 days); trilostane is administered daily.

ACE = angiotensin-converting enzyme; ACTH = adrenocorticotropic hormone; PDH = pituitary-dependent hyperadrenocorticism

* Vetoryl (dechra-us.com) is currently available only in 30 and 60 mg capsules in the U.S.