

PHARM PROFILE

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MITOTANE

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Mitotane (o,p'-DDD) is an antiadrenal agent used in the treatment of inoperable adrenocortical carcinoma in humans.¹ The drug is also used off-label in dogs to treat pituitary-dependent hyperadrenocorticism (PDH) and adrenal tumor hyperadrenocorticism (ATH).

PHARMACOLOGY

Mitotane exerts a direct cytotoxic effect on the adrenal cortex, resulting in selective, progressive necrosis and atrophy of the zona fasciculata and reticularis. The zona reticularis of the adrenal cortex is the most sensitive to the action of mitotane, whereas the zona glomerulosa is the least sensitive. Because of the relative resistance of the zona glomerulosa to the cytotoxic effects of mitotane, normal secretion of aldosterone is usually maintained.² In addition to its direct cytotoxic effects, mitotane interferes with steroid biosynthesis (although the exact mechanism of this effect is not known).³

Mitotane is a fat-soluble drug and thus should be given in food to increase bioavailability.² The drug is distributed to virtually all

tissues in the body and primarily stored in adipose tissue.⁴ Mitotane must be converted to its active form by the P-450 system to produce its effect. The exact metabolic fate of mitotane in dogs is not known. It is assumed to be similar to that in humans, in whom mitotane undergoes oxidative metabolism in the liver and is then excreted in the bile and urine.^{2,5}

INDICATIONS

In animals, mitotane has been used primarily for treatment of PDH and ATH in dogs.⁶ Hyperadrenocorticism in cats, although rare, can also be treated with mitotane. Surgery seems to offer greater success in cats than does mitotane. Therefore, mitotane therapy is usually limited to cats that are not surgical candidates or in which surgery has failed.⁷

CAUTIONS

Mitotane therapy is contraindicated in patients with a known hypersensitivity to the drug.⁸ Patients with diabetes or hepatic or liver disease should be monitored closely, and mitotane therapy in these patients should be used with caution.⁵

Adverse Reactions

The most common adverse reactions to mitotane therapy are gastric irritation and vomiting shortly after administration. To help mini-

mize these effects, the dose may need to be divided further, the time interval increased, or both.⁷ Giving mitotane with food may also help reduce some of the gastrointestinal adverse effects as well as increase absorption. Other common adverse effects include weakness, anorexia, diarrhea, and ataxia, which are signs of hypocortisolism. If these signs develop, glucocorticoid therapy is warranted and mitotane should be withheld until the signs resolve.^{7,9} In rare cases, mitotane may cause necrosis of the zona glomerulosa, resulting in hyponatremia and hyperkalemia secondary to mineralocorticoid deficiency. Animals with severe adverse reactions to mitotane should be checked for hypocortisolism with a corticotropin (ACTH) stimulation test, and serum electrolyte concentrations should be monitored. Treatment with intravenous fluids may be indicated.

Use in Pregnancy

It is unknown whether mitotane crosses the placenta or enters the milk. Mitotane should be used with caution in pregnant bitches, and it is suggested that puppies be given a milk replacer after receiving colostrum if the mother is receiving mitotane.⁵

Acute Toxicity

No specific guidelines have been

Client Counseling Information

- Possible adverse effects of mitotane therapy include nausea, vomiting, diarrhea, and weakness. If these adverse effects occur, the drug should be discontinued immediately and the veterinarian should be contacted.
- If serious adverse effects develop, glucocorticoid therapy may be needed (administration of replacement steroids should be understood by clients).
- Mitotane can be severely toxic. Do not crush tablets or open capsules. Wash hands after handling the medication.
- Give mitotane with food.
- Store the drug at room temperature and keep it out of reach of children and other pets.
- Administer the drug exactly as prescribed, and be sure to have the veterinarian monitor your pet's condition as scheduled.

developed for managing mitotane overdose. For recent ingestion, emptying the stomach and administering charcoal should be considered. The patient should be monitored closely and given glucocorticoids for treatment of signs of hypocortisolism, if necessary.⁵

DRUG INTERACTIONS

Mitotane is an inducer as well as a substrate of the hepatic microsomal enzyme system. Any drug that induces this system (e.g., phenobarbital) may decrease concentrations of mitotane, resulting in a diminished effect. These drugs may dramatically increase mitotane dosage requirements in dogs being treated for hyperadrenocorticism.²

Diabetic dogs receiving insulin may have insulin resistance secondary to hyperadrenocorticism. Treatment with mitotane will remove the cause of insulin resistance and reduce the daily insulin requirement. This may lead to insulin overdose and hypoglycemia.²

In dogs, spironolactone has been shown to block the action of mitotane⁵ (although the mechanism of this interaction is not known). One 65-year-old woman who was receiving spironolactone was placed on mitotane therapy for Cushing's disease that could not be managed surgically. After 5 months on both drugs, she showed

no signs of mitotane activity (i.e., no side effects or disease control). When the spironolactone was discontinued, symptoms indicative of mitotane therapy (e.g., severe nausea, profuse diarrhea) appeared within 24 hours.¹⁰

When mitotane is given concurrently with warfarin, the metabolism of both drugs may be increased.^{2,8}

DOSAGE AND ADMINISTRATION

Treatment of hyperadrenocorticism with mitotane in dogs consists of two phases: induction and maintenance. PDH is treated slightly differently than ATH.

Pituitary-Dependent Hyperadrenocorticism

Induction therapy for PDH is initiated at 40 to 50 mg/kg/day PO divided into two daily doses given with meals.⁹ The induction phase is usually complete when a decrease in appetite is noted or water consumption falls below 60 ml/kg/day.⁷ An ACTH stimulation test should be performed to confirm completion of the induction phase, which should take about 7 to 10 days.¹¹ The goal of this phase is for serum cortisol levels to be in the lower end of the normal range (1 to 4 µg/L or 25 to 125 nmol/L) before and after ACTH stimulation.¹² Glucocorticoids may be

needed during induction therapy if cortisol levels fall to subnormal levels (less than 25 nmol/L)¹¹ or if serious adverse effects develop.

Once a hypoadrenal result has been achieved, **maintenance therapy** may be initiated.⁷ Maintenance phase dosing should be started at 50 mg/kg/week PO given once weekly or in divided doses over the course of a week, if necessary.¹¹ An ACTH stimulation test should be performed at 1 and 3 months after initiation of maintenance therapy and every 3 to 6 months thereafter to assess therapy and adjust dose if needed.⁷ Maintenance therapy with mitotane is lifelong due to the underlying cause of the hyperadrenocorticism (i.e., pituitary tumor or dysfunction) not being addressed.

Adrenal Tumor

Hyperadrenocorticism

Surgery is the preferred treatment for ATH. Mitotane is used for dogs that are not surgical candidates or when surgery fails due to unrealized metastatic disease.

Induction therapy for ATH should be initiated at 50 to 75 mg/kg/day PO divided into two daily doses and given with meals for 10 to 14 days.¹¹ Concurrent prednisone supplementation at 0.2 mg/kg/day PO is indicated throughout the period on mitotane therapy. At the end of this initial daily administration, an ACTH stimulation test should be performed. Prednisone supplementation should be withheld on the morning of the test to avoid interference with the cortisol assay.¹¹ The goal of the induction phase is for cortisol levels to fall below normal.¹¹ If the initial dose is ineffective, the daily dose should be increased by 50 mg/kg/day every 10 to 14 days until cortisol levels fall below normal or drug intolerance develops. Cumulative induction doses for ATH

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may need to be up to 10 times those for PDH.¹¹

Once low cortisol levels have been achieved, an initial **maintenance dose** of 75 to 100 mg/kg/week PO in divided doses given with daily maintenance glucocorticoid should be initiated.¹¹ An ACTH stimulation test should be performed at 1 to 2 months after initiation of the maintenance phase and every 3 to 6 months thereafter to assess therapy and adjust dose if needed.¹¹

It has been noted that dogs with ATH are more resistant to the adrenocorticolytic effects of mitotane than are dogs with PDH.⁶ Dogs with ATH can be managed with mitotane but at a success rate below that of PDH.⁶

MONITORING

After a dog has received 8 or 9 days of induction therapy, mitotane should be withheld and an ACTH stimulation test performed. Mitotane should continue to be withheld until the results of the ACTH stimulation test are interpreted and further therapy can be decided. Blood urea nitrogen, liver enzyme, complete blood cell count, ACTH stimulation test (every 3 to 6 months), sodium, and potassium levels should be monitored periodically.¹³

PREPARATIONS

Mitotane (Lysodren[®], Bristol Laboratories Oncology Products, Princeton, NJ) is available as 500-mg tablets⁸ at a cost of \$279.80 per 100.¹⁴ There are currently no generic products available. Due to the limited dosage forms and the dosing scheme (mg/kg basis), mitotane needs to be compounded to provide accurate dosing. Pharmacists have the ability to compound mitotane capsules into any custom dose needed. Precautions need to be taken when compounding mitotane due to its potential toxicity when crushed and handled.

STORAGE AND HANDLING

Mitotane tablets may be stored at room temperature⁸ in air-tight, light-resistant containers. Washing hands after handling the drug is recommended due to the potential toxicity.

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