

**PROVEN THERAPY**

Research studies show that desoxycorticosterone pivalate injectable suspension is a safe and effective therapy for dogs with Addison's disease.

FOCUS ON

Desoxycorticosterone Pivalate for Dogs With Addison's Disease

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Desoxycorticosterone pivalate (DOCP) is a mineralocorticoid replacement therapy for dogs with primary hypoadrenocorticism (Addison's disease). This article covers its mechanism of action, dosing, monitoring, effectiveness, and safety and discusses clinical applications for both available formulations of the drug: Percorten-V (Elanco, elanco.com) and Zycortal (Dechra, dechra.com).

MECHANISM OF ACTION

DOCP is a long-acting analog of desoxycorticosterone, an endogenous steroid hormone and precursor to aldosterone. When administered parenterally, it produces the same physiologic effects as endogenous aldosterone, increasing sodium retention in the distal tubule and renal collecting ducts through active sodium resorption and upregulated sodium/potassium exchange.¹ Thus, DOCP increases serum sodium and chloride concentrations, promotes potassium excretion, and results in enhanced osmotic renal water retention. It is generally considered to have no glucocorticoid activity, though some have suggested weak activity,² and should be used in conjunction with appropriate glucocorticoid replacement therapy for Addisonian patients exhibiting both glucocorticoid and mineralocorticoid deficits. The manufacturers of both formulations recommend accompanying DOCP with

prednisone or prednisolone at a starting dose of 0.2 to 0.4 mg/kg/day.^{3,4}

FORMULATIONS

Percorten-V was approved for canine use by the U.S. Food and Drug Administration (FDA) in 1998, and Zycortal was approved for use by the European Medicines Agency in 2015 and the FDA in 2016. Both products contain 25 mg desoxycorticosterone per milliliter and are formulated as microcrystalline suspensions, allowing for slow dissolution and prolonged drug release.^{1,4} They differ in their use of preservative and surfactant.¹ Percorten-V is labeled for intramuscular injection but is often given subcutaneously in clinical practice. Zycortal is labeled for subcutaneous injection. Pharmacokinetic studies found that Zycortal demonstrated a longer half-life (17 days) when administered subcutaneously as opposed to intramuscularly (8 days).¹

EFFECTIVENESS

Two well-controlled clinical field trials found that, at doses of 2.2 mg/kg administered once every 25 days, Percorten-V provided good control of clinical signs of hypoadrenocorticism, resulting in normalization of serum sodium, potassium, and blood urea nitrogen

(BUN) concentrations, as well as body weight increases, although adjustments of the dose or dose frequency were sometimes needed.⁵

In a double-blind field trial, 152 dogs with primary adrenocortical insufficiency were randomized to treatment with either Percorten-V or Zycortal. Zycortal was found to be noninferior to Percorten-V in both management of clinical signs and control of serum sodium and potassium concentrations as evaluated at 90 days and 180 days after initiation of treatment.^{6,7}

SAFETY

Safety trials conducted by the manufacturer of Percorten-V concluded that DOCP was tolerated without significant morbidity or mortality at doses up to 15 times the recommended dose of 2.2 mg/kg when administered intramuscularly every 28 days to clinically normal beagles for a period of 6 months.^{5,8} Noted adverse effects included polyuria, polydipsia, decreased serum potassium and BUN concentration, decreased urine creatinine, and weight loss.⁸

Additional safety studies conducted by the manufacturer of Zycortal found no serious adverse effects in healthy beagles receiving up to 5 times the recommended treatment dose every 21 days for 6 months (9 injections).^{1,6} Treated dogs exhibited decreased urine specific gravity, increased serum sodium and globulins, and decreased serum potassium and BUN, consistent with the pharmacologic effects of the drug.^{1,6} Injection site reactions were the most common adverse effect.^{1,6}

In effectiveness field studies, commonly reported adverse events for both Percorten-V and Zycortal included polydipsia, polyuria, and inappropriate urination.^{5,6} In the Zycortal field effectiveness study, lethargy/depression was reported more commonly with Zycortal than Percorten-V (9.7% versus 2.6%), while diarrhea was reported more commonly with Percorten-V (7.7% versus 2.7%).⁶ Other adverse effects from field studies of both drugs included 1 dog with a preexisting heart murmur that developed congestive heart failure,⁶ 2 dogs with loss of hormonal control requiring a shorter dosage interval, and 1 dog that collapsed after the first dose, possibly from inadvertent intravenous drug administration.⁵

Both the Percorten-V and Zycortal product labels include cautions for use in patients with preexisting congestive heart failure, severe renal disease, or edema

(Percorten-V recommends not using the drug at all in these patients), and both products are not recommended for use in pregnancy.^{3,4} The Zycortal label also includes a caution for patients with primary hepatic failure.³

COMPARISON TO FLUDROCORTISONE ACETATE

An alternative mineralocorticoid replacement therapy, fludrocortisone acetate, is available for use in dogs with adrenal insufficiency. Fludrocortisone acetate is an oral mineralocorticoid typically given twice daily. In contrast to DOCP, it possesses significant glucocorticoid activity. Thus, in some patients treated with fludrocortisone, supplemental glucocorticoid therapy may not be needed. However, this additional glucocorticoid activity may contribute to dose-dependent adverse effects, including polyuria, polydipsia, and polyphagia. As DOCP has minimal glucocorticoid activity, its dose and dosing interval can be adjusted to effect without affecting glucocorticoid delivery.

Studies comparing the effectiveness of DOCP and fludrocortisone are limited. The available data suggest the 2 drugs provoke a similar clinical response; patients that have persistent polyuria/polydipsia when treated with fludrocortisone may experience fewer adverse effects from DOCP. A 1997 study of 200 dogs with primary hypoadrenocorticism found no significant difference in clinical response to treatment or median survival times between patients treated with DOCP and patients treated with fludrocortisone.⁹ However, treatment was changed from fludrocortisone to DOCP in 27 dogs due to the development of adverse effects, poor clinical response, or owner convenience/finances.⁹

A 2014 study compared plasma renin activity (PRA) in dogs with hypoadrenocorticism treated with fludrocortisone or DOCP.¹⁰ PRA is considered the gold standard in human medicine for monitoring response to mineralocorticoid therapy, as it is increased in people with adrenocortical insufficiency and decreases with mineralocorticoid replacement therapy. In studied dogs, increased baseline PRA levels normalized after treatment with DOCP but not with fludrocortisone. Serum sodium and potassium were also more commonly in the reference range in dogs treated with DOCP. Five dogs were switched from fludrocortisone to DOCP due to adverse glucocorticoid effects or poor clinical response to treatment.¹⁰

Most clinicians consider DOCP the preferred mineralocorticoid for replacement therapy in dogs with hypoadrenocorticism, although fludrocortisone is a reasonable option for owners when oral therapy is strongly preferred or DOCP injections are not tolerated.

DOSING AND MONITORING

DOCP dosing protocols are tailored to the individual based on clinical response to therapy after administration of an initial starting dose. Package inserts for Percorten-V and Zycortal differ slightly in their dosing and monitoring recommendations, and existing clinical studies have taken varied approaches to dose adjustment in their studied patient populations.

Manufacturer Recommendations

Both Percorten-V and Zycortal are labeled for a starting dose of 2.2 mg DOCP/kg body weight, administered once every 25 days.^{3,4} Elanco recommends evaluating serum electrolytes at 14 days and 25 days after administration of Percorten-V. Patients are considered well controlled, with no adjustments recommended to dose or dosing interval, if serum electrolyte levels are normal or only slight hyponatremia and slight hyperkalemia exist at both 14 and 25 days. In dogs with more significant hyperkalemia or hyponatremia, guidelines state that the dosage interval should be decreased by 2 to 3 days. Elanco advises that most patients are well controlled with a dose range of 1.65 to 2.2 mg/kg given every 21 to 30 days.⁴ Dechra recommends serum sodium/potassium ratios be measured at 10 and 25 days after initial administration of Zycortal to determine changes in recommended dose and dosing interval, as described in the package insert.³

Alternative Adjustment Protocols

Alternative monitoring and dose adjustment protocols have been described in the literature. In most described protocols, serum electrolyte (sodium and potassium) concentrations are measured at 2 time points after initial injection. Concentrations measured at the first time point (typically 10 to 14 days postinjection) are used to determine necessary dosage adjustments, while those measured at the second time point (typically 25 to 30 days postinjection) are used to determine necessary changes in dosing interval.

A 2010 review suggests that, if hyperkalemia or hyponatremia is present at the initial recheck (day 12),

the next DOCP dose should be increased by 5% to 10%, while if hypokalemia or hypernatremia is present, the next dose should be decreased by 5% to 10%. If the patient is hyperkalemic or hyponatremic at the subsequent recheck (day 25), the dosing interval can be decreased by 1 day.¹¹ Other authors allow for further dosage reduction and interval extension in a clinically normal patient to allow for titration to the lowest effective dose.¹⁰ Following establishment of a maintenance dose and dosing interval, subsequent monitoring of electrolyte levels once every 3 to 6 months is typically recommended.

Alternative Dosing Protocols

As primary hypoadrenocorticism necessitates lifelong mineralocorticoid replacement therapy, cost of treatment is often a significant hurdle to delivery of care. Also, excessive mineralocorticoid supplementation may have deleterious effects. A number of studies have evaluated alternative dosing regimens in an attempt to characterize the success of lower-cost and lower-dose protocols in controlling clinical signs of disease. These studies have demonstrated that good clinical control of disease can be achieved for many patients at doses lower than the 2.2 mg/kg starting dose recommended by the manufacturers.

Dose Reduction

A 2019 prospective study of 17 dogs with newly diagnosed primary hypoadrenocorticism found that a starting dose of 1.5 mg/kg of Zycortal was sufficient to control clinical signs and maintain normal serum electrolyte concentrations in all but 2 patients.¹² Further dosage reductions were used to achieve an injection interval of 28 to 30 days (median dose at 2 to 3 months, 1.1 mg/kg) in most dogs, and no dogs required the recommended 2.2 mg/kg dose. Further analysis of these results suggested that young, growing dogs might require higher initial doses that can be reduced over time.¹²

A similar retrospective study of 13 dogs with primary hypoadrenocorticism found a 1.5 mg/kg starting dose to be effective in all but 1 dog that required a dose of 1.6 mg/kg.¹³ A 2013 retrospective study of 49 dogs found that initial DOCP doses less than 2.2 mg/kg were effective at controlling clinical signs of hypoadrenocorticism, with a mean final dose of 1.3 mg/kg.¹⁴ In the 1997 study comparing DOCP with fludrocortisone, only 18% of the 33 dogs treated with

DOCP required doses of 2.2 mg/kg or higher, with a final median dose of 1.69 mg/kg and a median dosing interval of 30 days.⁹

Dosing Interval Extension

Extending the interval between doses is another approach to reducing cost of treatment, and recent evidence suggests that a longer dosing interval may still achieve effective disease control. A 2017 prospective clinical trial of 53 dogs found that the duration of action of DOCP (1.4 to 2.6 mg/kg/dose) ranged from 32 to 94 days (median, 62 days) in dogs with newly diagnosed primary hypoadrenocorticism and from 41 to 124 days (median, 67 days) in dogs that had received previous treatment. The study concluded that a final acceptable treatment interval that maintained serum potassium and sodium concentrations within the reference interval for all studied patients ranged from 38 to 90 days (median, 58 days).¹⁵

Although this approach is effective, some clinicians prefer to prioritize dose reduction since owner compliance may be higher with more standard monthly drug administration.

CONCLUSION

DOCP is a safe and effective mineralocorticoid replacement therapy when used in dogs with primary hypoadrenocorticism. Recent research suggests that lower doses and longer dosing intervals than those

recommended in manufacturer guidelines may, for many patients, remain effective in controlling both serum electrolyte levels and clinical signs of disease. No current consensus exists regarding the most effective monitoring and dosing protocols. Further research is needed to better characterize clinically appropriate starting doses and evaluate the efficacy of the various dose adjustment and monitoring protocols used in clinical practice. **TVP**

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