



Randomised clinical non-inferiority trial comparing two formulations of desoxycortone pivalate for the treatment of canine primary hypoadrenocorticism

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Abstract

Background This clinical trial compared two formulations of desoxycortone pivalate (DOCP) for treating the mineralocorticoid deficit in dogs with primary hypoadrenocorticism (PH).

Methods At veterinary clinics in the USA and France, dogs with PH (n=152) were randomised (3:1) to receive approximately monthly treatments with either the test product, Zycortal (Dechra), administered subcutaneously (n=113), or the control product, Percorten-V (Novartis Animal Health), administered intramuscularly (n=39), both at an initial dose of 2.2 mg/kg DOCP. Treatment administrators were unblinded; veterinarians assessing clinical signs were blinded; owners were blinded until at least day 90, the primary end point. Veterinarians assessed treatment outcome based on all of the following: clinical signs; sodium concentrations; potassium concentrations. Dogs received concurrent glucocorticoid therapy throughout the trial. Non-inferiority was assessed using a generalised linear mixed model to compare success rates between groups.

Results Success rates at day 90 were similar between groups (per-protocol population at day 90: Zycortal 87/101, 86.2 per cent, Percorten-V 29/34, 85.1 per cent). Zycortal was non-inferior to Percorten-V as the upper limit of the 95 per cent CI for the difference between groups was 13.6 per cent. Polydipsia and polyuria were the most common clinical observations.

Conclusion Both products, in combination with glucocorticoid therapy, were safe and effective in treating PH.

Introduction

Primary hypoadrenocorticism (PH) is a deficiency of mineralocorticoid (primarily aldosterone) and/or glucocorticoid (primarily cortisol) secretion from the adrenal gland. Hypoaldosteronism leads to hyponatraemia and hyperkalaemia, causing dehydration, prerenal azotaemia and hypovolaemia. Hypocortisolaemia causes decreased stress tolerance, anaemia and hypoglycaemia. Non-specific clinical signs, such as lethargy, weakness,

dehydration, poor appetite, vomiting and diarrhoea, may wax and wane. Untreated PH can progress to vascular collapse and shock ('Addisonian crisis'). Hyperkalaemia and hyponatraemia, in combination with adrenocorticotrophic hormone stimulation test (ACTHst) results of minimal basal and poststimulation cortisol concentrations are diagnostic of PH.^{1 2} PH is treated by life-long replacement of the deficient hormones. Desoxycortone pivalate (DOCP) can be used for mineralocorticoid replacement therapy in combination with glucocorticoid replacement therapy of either prednisone or prednisolone. Occasional cases of PH are deficient only in glucocorticoids.¹ Fludrocortisone acetate may be used as a replacement for both mineralocorticoids and glucocorticoids in dogs with PH.³

This trial was performed to gain regulatory approval with the European Medicines Agency (EMA), and the US Food and Drug Administration (FDA) for

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Table 1 Eligibility criteria

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> ▶ Client-owned dog (not a stray or shelter animal) ▶ Manageable and cooperative with trial procedures ▶ Within 7 days of the time of laboratory diagnosis, ≥ 1 clinical sign(s) of: vomiting, diarrhoea, lethargy, inappetence, polyuria/polydipsia, dehydration, weakness/collapse ▶ At diagnosis, basal and post-ACTHst cortisol concentrations ≤ 55.2 nmol/l ▶ At diagnosis, Na/K ratio was $\leq 27^{19}$; newly diagnosed dogs could enrol with a ratio of ≤ 24 while ACTHst results were pending, but were withdrawn from the trial if the ACTHst result was not as required 	<ul style="list-style-type: none"> ▶ Was participating in another trial with another investigational product. ▶ Pregnancy, lactation. ▶ Was anaesthetised with etomidate within 30 days of the diagnostic ACTHst. ▶ Received a corticosteroid before the diagnostic ACTHst: ≤ 14 days for topical or oral steroids, ≤ 30 days for parenteral steroids (except dexamethasone for emergency treatment of acute PH crisis), ≤ 24 hours for dexamethasone. ▶ Ever previously treated with Percorten-V. ▶ Iatrogenic hypoadrenocorticism. ▶ Already receiving treatment for another endocrine disease. ▶ Renal failure (prerenal azotaemia which resolved by fluid therapy was not exclusionary). ▶ Clinical signs of primary hepatic failure, congestive heart failure or oedema from any cause other than PH. ▶ Being treated with a medication which could interfere with the treatment of PH, eg, trimethoprim, amphotericin B, potassium-depleting diuretics.

ACTHst, adrenocorticotrophic hormone stimulation test; Na/K, sodium/potassium; PH, primary hypoadrenocorticism.

Zycortal Suspension (Dechra), a novel formulation of DOCP. The trial determined whether the safety and efficacy of Zycortal administered subcutaneously was non-inferior to the intramuscularly administered positive control product, Percorten-V Suspension (Novartis Animal Health), as a replacement therapy for the mineralocorticoid deficiency in dogs with PH. Percorten-V is approved by FDA for administration intramuscularly for this indication. As PH can progress to Addisonian crisis and death, a placebo-controlled trial would not have been ethical.

Materials and methods

This trial complied with all applicable animal welfare regulations related to the humane care and use of animals, and VICH GL9, *Good Clinical Practice*. Before trial initiation, FDA approval was received for the trial.

Participants

Veterinarians at veterinary clinics (either first opinion or specialty practices) in the USA and France enrolled dogs into this trial. Owners gave written informed consent for their dog's participation before the performance of any trial-related procedures, and could withdraw their dog from the trial at any time. To be enrolled into the trial, dogs had to meet all of the eligibility criteria described in [table 1](#).

Dogs eligible for enrolment included dogs newly diagnosed with hypoadrenocorticism, and dogs which had been diagnosed previously and were being treated with fludrocortisone or desoxycortone acetate (Syncortyl, Sanofi-Aventis France) before the start of the trial.

Interventions

All dogs were administered aqueous suspensions of DOCP, with a DOCP concentration of 25 mg/ml, in one of two formulations: group Z were administered the test article, Zycortal, subcutaneously; group P dogs were administered the control product, Percorten-V, intramuscularly. As replacement for their glucocorticoid deficiency, all dogs received either prednisone or

prednisolone throughout the trial at an initial dose of 0.1–0.5 mg/kg/day.

At each visit, before the administration of any trial medication, the concentration of sodium (Na) and potassium (K) in the serum or plasma was assessed, along with the sodium:potassium (Na/K) ratio and the dog's clinical signs related to hypoadrenocorticism. Na and K concentrations were measured at each clinic ('in-house').

On day 0, the first DOCP dose of 2.2 mg/kg was administered. Subsequent visits were scheduled to occur on days 10 (± 3 days), 25 (± 3 days), 60 (± 14 days), 90 (± 14 days) and 180 (± 14 days).

On day 25, results from both the day 10 and day 25 visits were used to determine the dose of DOCP to be administered. At day 25, if the dog was clinically normal and had an Na/K ratio of 27–32, then the DOCP dose was chosen based on the day 10 Na/K ratio: up to 32, dose decreased; 27 to less than 32, no change; less than 27, dose increased. For clinically normal dogs with a day 25 Na/K ratio greater than 32, the veterinarian could alternatively choose to postpone the dose, and to re-check electrolytes weekly until the Na/K ratio was less than 32, when 2.2 mg/kg DOCP was administered.

If, on day 25, the dog was not clinically normal or the day 25 Na/K ratio was not 27–32, then the doses of DOCP and/or glucocorticoids were adjusted as follows: polyuria/polydipsia, polyphagia or panting, glucocorticoid dose decreased, 2.2 mg/kg DOCP administered; depression, lethargy, vomiting, diarrhoea or weakness, glucocorticoid dose increased; hyperkalaemia, hyponatraemia or Na/K ratio less than 27, DOCP dose increased or the interval to the subsequent dose decreased by two to three days; hypokalaemia, hypernatraemia or Na/K ratio greater than 32, DOCP dose decreased or dose postponed for three to seven days.

For the third and subsequent administrations of DOCP, if the dog was clinically normal and the Na/K ratio was 27–32, then the same DOCP dose and dosing interval was maintained as for the most recent dose. If this was not the case, then the dose of DOCP and/

or glucocorticoid was adjusted as described for day 25, with the additional guideline that the DOCP dose should be decreased if the dog had persistent polyuria/polydipsia combined with an Na/K ratio greater than 32.

The final trial day was at day 180, or the day of the sixth administration of DOCP, whichever was earlier.

On days 25, 90 and 180, blood samples collected before DOCP administration were analysed for haematology and serum chemistry parameters (including Na and K, at PRL Central Laboratories, Kansas, USA, or at Laboratoire IDEXX Alfort, Alfortville, France).

Medications which may have confounded the treatment or evaluation of PH were prohibited. Dogs which had been previously treated for PH with either fludrocortisone or desoxycortone acetate could continue treatment until day 0 (for fludrocortisone) or day -1 (for desoxycortone acetate).

Outcomes

Baseline data were collected during the enrolment phase in the seven days before day 0.

The primary effectiveness end point was at day 90, with a secondary end point at day 180. The effectiveness evaluation comprised the veterinarian's clinical assessment (CA) and measurement of Na and K concentrations. To perform the CA, the veterinarian compared the baseline signs of PH, Na and K concentrations, and Na/K ratio with these parameters on the day of assessment. Dogs which had signs of hypoadrenocorticism at the start of the trial were assigned an outcome of either *improved* or *not improved* (which included worsening of signs). Cases previously treated with fludrocortisone or desoxycortone acetate which had no clinical signs of PH at baseline were assigned an outcome of either *remained clinically normal* or *did not remain clinically normal*. Treatment success occurred when the CA was *improved* or *remained clinically normal*, and either of the following two criteria were met: the in-house Na and K concentrations were both within the reference range of the analyser or the Na/K ratio was 27–32 (inclusive). Exit of a dog from the trial due to a DOCP-related adverse event constituted a treatment failure.

Clinical pathology data and adverse events were analysed in all dogs administered at least one dose of DOCP. Clinical pathology data were evaluated by repeated measures analysis of covariance, with baseline values as a covariate. The statistical model included treatment, time and time by treatment interaction as fixed effects, site and all interactions with site as random effects and a suitable covariance structure. A separate analysis was conducted for the analytical laboratory results from each country ($\alpha=0.10$). This significance level ensured that more safety variables would be flagged for assessment of clinical relevance

than would occur with a more standard significance level (such as $\alpha=0.05$). The higher a value increases the probability of a type I error, but reduces the probability of failing to detect a true difference in safety variables which may be of concern. An adverse event was defined as any observation, whether or not considered to be product related, that is unfavourable and unintended and that occurred during the trial on or after day 0. A serious adverse event was defined as any adverse event which resulted in death, was life threatening, or resulted in persistent or significant disability/incapacity. The veterinarian assessed the relationship of each adverse event to the trial medication, and assigned a causality assessment of either probable, possible, unknown, or unlikely.

Sample size

Sample size was determined using the following parameters: probability of type I error (α): 0.05; probability of type II error (β): 0.20; expected success rate of group Z: 90 per cent; expected success rate of group P: 90 per cent^{4,5}; margin of difference (Δ): 15 per cent; experimental unit: one dog; weighted number in the test article group: 3; total sample size: 133 dogs, of which group Z: 100 dogs; group P: 33 dogs.

Randomisation, blinding, and treatment allocation

The statistician generated a randomisation sequence using the PLAN procedure in SAS (v.12.1, SAS Institute, Cary, North Carolina, USA). Blocking was based on order of enrolment at each trial site, with eligible dogs randomised to one of two treatment groups, in a ratio of 3 test article to 1 control product, in a parallel design. At each site, an unblinded treatment administrator allocated animals to a group, and administered the DOCP. This person was not involved in animal enrolment or assessment, and had sole access to the randomisation sequence. Blinding was not possible for the treatment administrator as the route of administration differed between groups. Veterinarians assessing the cases, laboratory personnel and the biostatistician were blinded to the treatment group assignments until data collection was complete. Owners were blinded even after trial completion, except those who accepted the offer (made at the veterinarian's discretion) to administer DOCP doses at home following the day 90 visit.

Statistical methods

Non-inferiority of the test article to the control product was evaluated by calculating a two-sided 95 per cent CI on the difference between the treatment success rates of the two groups using a generalised linear mixed model (the GLIMMIX procedure in SAS V.12.1); treatment group was included as a fixed effect in the model, and trial site and site-by-treatment interaction were included as random effects. A binomial

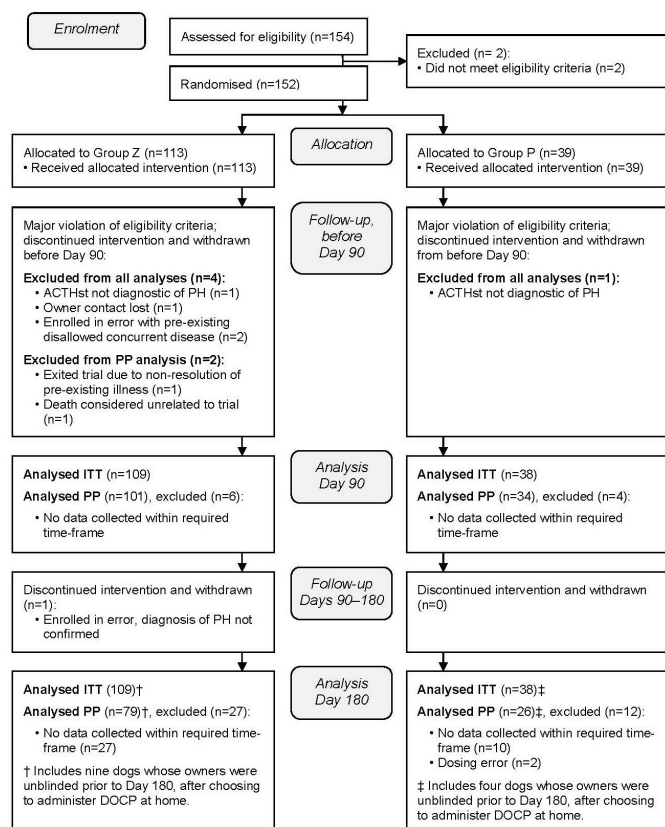


Figure 1 Flow of participants through the study, showing number of dogs evaluated at each time point. ACTHst, adrenocorticotropic hormone stimulation test; DOCP, desoxycortone pivalate; ITT, intention-to-treat; PH, primary hypoadrenocorticism; PP, per-protocol.

distribution was assumed, and a logit link used. For Zycortal to be non-inferior to Percorten-V, the lower bound of this CI had to be within the set margin (15 per cent).

The per cent success and lower bound of the 95 per cent CI for the treatment success rate of group Z was calculated to demonstrate effectiveness for the EMA, since the control product is not approved in the EU.

Two populations were evaluated, an intention-to-treat (ITT) population (per the EMA's *Guideline on statistical principles for clinical trials for veterinary medicinal products (pharmaceuticals)*, effective 2012), and a per-protocol (PP) population. Dogs were excluded from the ITT population in the case of major eligibility violations, failure to receive at least one dose of trial drug or lack of postrandomisation data. In case of missing data in the ITT evaluations, the last observation was brought forward. Dogs were excluded from the PP population evaluated at each time point due to non-compliance with the protocol or lack of data collected during the required time period; the decision to exclude dogs from the PP population was made before unblinding occurred. In case of missing data in the PP effectiveness evaluation, the last observation was not brought forward.

Demographic and dose administration data are presented as mean±sd. Summary statistics related to the dosages of DOCP and glucocorticoid administered during the trial were calculated in the PP population.

Table 2 Summary of baseline demographic characteristics of all enrolled dogs

	Group Z	Group P	All dogs
Demographic characteristics			
Dogs enrolled, n (%)	113 (74.3)	39 (25.7)	152
Body weight, kg Mean±sd (range)	23.1±14.6 (1.0–61.2)	21.1±14.7 (2.0–59.0)	22.5±14.6 (1.0–61.2)
Age, years Mean±sd (range)	4.8±2.7 (0.5–12.4)	4.5±2.9 (0.5–9.8)	4.7±2.7 (0.5–12.4)
Sex, n (%)			
Female entire	5 (4)	5 (13)	10 (7)
Female neutered	51 (45)	17 (44)	68 (45)
Male entire	4 (4)	5 (13)	9 (6)
Male neutered	53 (47)	12 (31)	65 (43)
Breed, n (%)			
Mixed	43 (38)	11 (28)	54 (36)
Poodle	9 (8)	1 (3)	10 (7)
Labrador retriever	6 (5)	1 (3)	7 (5)
West Highland white terrier	5 (4)	2 (5)	7 (5)
Other	50 (44)	24 (62)	74 (49)
Previous treatment for PH, n (%)			
Fludrocortisone	31 (27)	13 (33)	44 (29)
Desoxycortone acetate	2 (2)	0	2 (1)
None	80 (65)	26 (67)	106 (70)
Group Z: treated with Zycortal. Group P: treated with Percorten-V. n (%): number (percentage) of dogs in each group.			

Results

From February 2012, 154 dogs were evaluated for eligibility from 13 veterinary clinics in the USA and two veterinary clinics in France, with the final dog exiting the trial in September 2013. Two dogs were ineligible for enrolment, resulting in 152 dogs being allocated to a treatment group (figure 1). The baseline demographic information for all enrolled dogs is summarised in table 2. The baseline electrolyte values of the ITT population are summarised in table 3.

Nine owners in group Z and four in group P were unblinded when they opted to administer the DOCP dose at home after day 90. One owner in group Z reported difficulty administering the entire dose to their dog; the other 12 owners who administered DOCP at home did not report any problems.

The final DOCP dose for group Z was 1.94±0.27 mg/kg (range 1.15–2.53), and for group P was 1.96±0.27 mg/kg (range 1.39–2.80). The final dose interval was 38.7±12.7 days (range 20–99) for group Z, and 42.4±25.8 days (range 23–50) for group P. One dog in group P had only one dose of DOCP during the 182 days that it was enrolled in the trial since its Na/K ratio remained ≥33. For both groups, the mean initial glucocorticoid dose was 0.4±0.4 mg/kg/day (range 0.02–3.45), and the final dose was 0.1±0.1 mg/kg/day (range 0.01–0.51) with 91 (86 per cent) dogs in group Z, and 37 (97 per cent) dogs in group P having a reduced dose at day 180.

Effectiveness outcomes

The participant flow diagram (figure 1) shows the progress of dogs through the trial and reasons for

Table 3 Summary of baseline sodium (Na) and potassium (K) values for dogs included in the intention-to-treat population

	Group Z	Group P
Number of dogs evaluated	109	38
Na concentrations below the reference range's lower limit, n (%)*	83 (76)	25 (66)
K concentrations above the reference range's upper limit, n (%)*	86 (79)	29 (76)
Na/K ratio \leq 27, n (%)†	94 (86)	33 (87)

n (%): number (percentage) of dogs in each group.
 *Reference range of the in-house analyser at each site.
 †For cases previously treated for PH, Na/K was required to be \leq 27 at time of diagnosis, rather than at baseline.

non-evaluability at each time point. Results are summarised in [table 4](#).

At day 90, the upper CI for the difference between groups was 13.6 per cent (PP population) and 13.8 per cent (ITT population); therefore, the test article was non-inferior to the control product. To determine treatment outcome without reference to group P, the lower bound of the 95 per cent CI for group Z success was estimated as 77.8 per cent (PP population) and 76.2 per cent (ITT population). In the PP population, the veterinarian's CA evaluated 100 group Z dogs (99 per cent) and 34 group P dogs (100 per cent) as a treatment success.

At day 180, the upper confidence limit for the difference between groups was 18.3 per cent in the PP population (higher than the 15 per cent cut-off for non-inferiority), but 13.8 per cent in the ITT population. Therefore, although the per cent success was higher for group Z than for group P in both the ITT and PP analyses, non-inferiority between groups was demonstrated only in the ITT population. To determine treatment outcome without reference to group P, the lower bound of the 95 per cent CI for group Z success was estimated as 78.0 per cent (PP population) and 78.3 per cent (ITT population). In the PP population, the veterinarian's CA evaluated all dogs in both groups as a treatment success.

Exploratory analyses

On day 0, the majority of dogs in both groups had low Na concentrations ([figure 2](#)), high K concentrations ([figure 3](#)), and a low Na/K ratio ([figure 4](#)). By day 90,

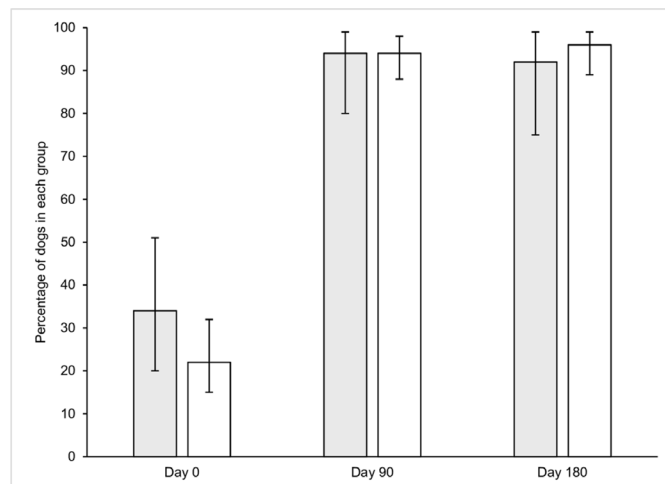


Figure 2 Percentage of dogs with sodium concentrations within the in-house reference range before DOCP administration (day 0), and at days 90 and 180 after DOCP treatment, showing the 95% CI group P (Percorten-V treated): grey; group Z (Zycortal treated): white. DOCP, desoxycortone pivalate.

and at day 180, the Na and K concentrations for both groups were within reference range for at least 89 per cent of dogs, whereas the Na/K ratio was within the required range for fewer than 25 per cent of dogs ([table 5](#)). The percentage of dogs with an Na/K ratio within the required range was numerically but not statistically higher in group P. By day 90, the majority of dogs in both groups had Na/K ratios above the target range ([table 6](#)).

Safety evaluation

All 152 enrolled dogs were included in the safety assessment, 113 in group Z and 39 in group P.

The most frequently reported abnormal clinical signs in both groups are listed in [table 7](#), along with the proportion determined by the veterinarian to be probably or possibly related to treatment with DOCP. Except as detailed below, these signs resolved either spontaneously or with supportive care, and did not require cessation of DOCP treatment.

Three serious adverse events were reported in group Z. An 11-month-old Chihuahua was suddenly found dead on day 50, 10 days after the third DOCP dose. The owner reported the dog had been normal the previous evening; postmortem examination did not establish

Table 4 Primary effectiveness outcome and veterinarian's CA of each group and each analysed population

Day	Analysis set	Group Z		Group P	
		Per-protocol	Intention-to-treat	Per-protocol	Intention-to-treat
90	Number of dogs evaluated	101	109	34	38
	Treatment success, n (%)	87 (86.2)	92 (84.6)	29 (85.1)	32 (84.1)
	Veterinarian's CA, success, n (%)	100 (99.0)	107 (98.2)	34 (100)	38 (100)
180	Number of dogs evaluated	79	109	26	38
	Treatment success, n (%)	69 (88.3)	94 (86.5)	23 (86.9)	32 (84.3)
	Veterinarian's CA, success, n (%)	79 (100)	108 (99.1)	26 (100)	26 (100)

Group Z: treated with Zycortal.
 Group P: treated with Percorten-V.
 n (%): number (percentage) of dogs in each group.
 *Back-transformed from the least squares means of the logit transformation.
 CA, clinical assessment.

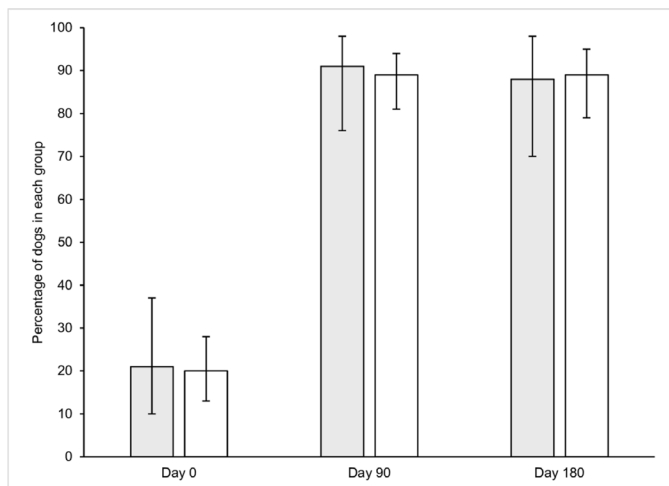


Figure 3 Percentage of dogs with potassium concentrations within the in-house reference range before DOCP administration (day 0), and at days 90 and 180 after DOCP treatment, showing the 95% CI group P (Percorten-V treated): grey; group Z (Zycortal treated): white. DOCP, desoxycortone pivalate.

cause of death. A seven-year-old Maltese with a pre-existing grade III/VI holosystolic heart murmur was diagnosed with congestive heart failure on day 17 and exited the trial, as congestive heart failure was an exclusion criterion. An old English sheepdog (aged 10 years) was enrolled into the trial with newly diagnosed PH, with vomiting, diarrhoea, dehydration, weakness/collapse, lethargy and inappetence. Five hours after the first DOCP dose, the dog had acute onset haematemesis and melaenic diarrhoea followed by pyrexia, vasculitis and sepsis. With supportive therapy, the dog made a full recovery and these events did not recur following five subsequent DOCP doses. The examining veterinarians considered these events to have an unknown or unlikely relationship to DOCP administration. No serious adverse events were reported in group P.

The mean values for all haematology and biochemistry analytes in both groups fell within the laboratories' reference ranges at days 90 and 180. While within the reference range, values for calcium, phosphorus, blood urea nitrogen and monocytes were

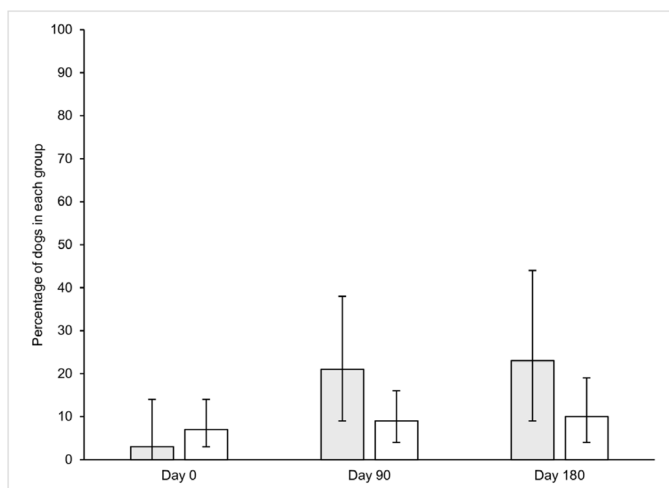


Figure 4 Percentage of dogs with sodium:potassium ratio within the required range of 27–32 before DOCP administration (day 0), and at days 90 and 180 after DOCP treatment, showing the 95% CI group P (Percorten-V treated): grey; group Z (Zycortal treated): white. DOCP, desoxycortone pivalate.

significantly ($P < 0.10$) lower in group Z than group P in the USA. In France, there were no significant differences ($P < 0.10$) between the groups for any analyte at any time point.

Three elective surgeries were performed during the trial: one castration (group P), one ovariohysterectomy (group Z) and one cruciate repair (group Z).

Discussion

Limitations

Ideally, new medicinal products should be compared with a placebo control. However, as PH is ultimately fatal, the use of a placebo control in this trial would have been ethically unacceptable and so a positive control was used instead. The positive control product has been approved in the USA for the treatment of PH since 1998,⁶ and its use is supported by previous studies,^{5,7} although these studies were not placebo-controlled. Fludrocortisone is commonly used to treat PH in dogs; however, as it has glucocorticoid actions not found in DOCP,³ it would not have been a suitable comparator.

Determination of success depended on the clinical assessment, in combination with the Na and K concentrations or the Na/K ratio. More dogs in both groups had a favourable clinical assessment of 'improved' or 'remained clinically normal' than were determined a treatment success. The incorporation of the Na and K results into the definition of success added methodical rigour but may have led to the underestimation of the effectiveness of DOCP as replacement therapy for the mineralocorticoid deficit in dogs with PH.

Generalisability

The demographics of the trial population were consistent with previous descriptions of dogs with PH; the majority of dogs were neutered and young to middle-aged. There were approximately equal numbers of each sex; in other studies, females have been over-represented.^{1,4,8-11} In this trial, poodles were the most common breed; this is not unexpected as it has previously been reported that poodles are disproportionately diagnosed with PH.^{1,4,11}

Interpretation

Percorten-V is approved for intramuscular administration, although subcutaneous administration has been reported.¹ Zycortal is approved for subcutaneous administration and owners can potentially administer it at home. This trial, along with others, supports the initial label dosage of Percorten-V and Zycortal of 2.2 mg/kg of DOCP.¹⁵ Using separate products for mineralocorticoid and glucocorticoid replacement allows the dosage of each to be individualised. This is not possible with fludrocortisone; at a fludrocortisone dosage adequate

Table 5 In-house serum sodium (Na) and potassium (K) concentrations, and Na/K ratio results at each time point

Day	Group	N	Na concentrations		K concentrations		Na/K ratio	
			N (%)	95% CI	N (%)	95% CI	N (%)	95% CI
0	Z	107	24 (22.4)	14.9 to 31.5	21 (19.6)	12.6 to 28.4	8 (7.5)	3.3 to 14.2
	P	38	13 (34.2)	19.6 to 51.4	8 (21.1)	9.6 to 37.3	1 (2.6)	0.1 to 13.8
90	Z	101	95 (94.1)	87.5 to 97.8	90 (89.1)	81.4 to 94.4	9 (8.9)	4.2 to 16.2
	P	34	32 (94.1)	80.3 to 99.3	31 (91.2)	76.3 to 98.1	7 (20.6)	8.7 to 37.9
180	Z	79	76 (96.2)	89.3 to 99.2	70 (88.6)	79.5 to 94.7	8 (10.1)	4.5 to 19.0
	P	26	24 (92.3)	74.9 to 99.1	23 (88.5)	69.9 to 97.6	6 (23.1)	9.0 to 43.7

Group Z: treated with Zycortal.
Group P: treated with Percorten-V.
n (%): number (percentage) of dogs in each group with results within the required ranges: reference range of the in-house analyser at each site (Na and K concentrations) or 27–32, inclusive (Na/K ratio).
.N, number of dogs evaluated in each group at each time point.

to replace the mineralocorticoid deficiency, the glucocorticoid deficiency may be overcompensated so that signs of iatrogenic hypercortisolism (polyuria/polydipsia, polyphagia) occur.⁵

As glucocorticoids were administered concurrently with DOCP, it was not always possible to determine whether polyuria and polydipsia were associated with the glucocorticoid, with DOCP, or with both medications. Polyuria and polydipsia occur following prednisone administration in dogs,¹² but excessive DOCP administration (2.2 mg/kg once daily for three days every 28 days) also causes polydipsia.¹³ The physiological replacement dose of cortisol in dogs equates to 0.1–0.2 mg/kg/day of prednisolone or prednisone.¹⁴ Doses greater than the physiological replacement dose are recommended in the acute management of hypoadrenocorticism.³ The maintenance dose should be gradually tapered to the lowest dose which will control the clinical signs associated with glucocorticoid deficiency.³ In this trial, the protocol did not require the initial glucocorticoid dose (0.1–0.5 mg/kg/day) to be tapered; this may have influenced the occurrence of polyuria, polydipsia, inappropriate urination and polyphagia.

The relatedness of the serious events to DOCP administration is also difficult to determine. Haematemesis and melaenic diarrhoea, as displayed by the old English sheepdog on the first day of DOCP treatment, has previously been reported as an initial presenting sign in a dog with PH.¹⁵ The congestive heart failure in a dog with a pre-existing heart murmur may

Table 6 Summary of in-house sodium (Na)/potassium (K) ratios at each time point, by group

Day	Group	N	Na/K <27 n (%)	Na/K 27–32 n (%)	Na/K >32 n (%)
0	Z	107	95 (89)	8 (7)	4 (4)
	P	38	35 (92)	1 (3)	2 (5)
90	Z	101	2 (2)	9 (9)	90 (89)
	P	34	0	7 (21)	27 (79)
180	Z	79	0	8 (10)	71 (90)
	P	26	0	6 (23)	20 (77)

Group Z: treated with Zycortal.
Group P: treated with Percorten-V.
n (%): number (percentage) of dogs with values within the stated ranges.
N, number of dogs evaluated in each group at each time point.

have been due to blood volume expansion following DOCP and/or glucocorticoid administration. Mitral regurgitation in dogs may progress to congestive heart failure, particularly if the regurgitation is severe.

Fludrocortisone has a half-life of approximately 11 hours in dogs¹⁶; for treatment of PH, it is administered orally once or twice daily.¹⁷ It has been suggested that, when changing dogs from treatment with fludrocortisone to treatment with DOCP and a glucocorticoid, fludrocortisone treatment should be continued following the first administration DOCP, and then gradually tapered down over a few days.¹⁸ In this trial, fludrocortisone was discontinued immediately before DOCP administration in all 44 dogs which had been previously treated with fludrocortisone. In an earlier study, 43/60 dogs received fludrocortisone until immediately before administration of the first DOCP dose, with a similar efficacy and safety profile as is reported here.⁵ This suggests that continuing fludrocortisone after the first administration of DOCP may not be required.

During this trial, Na and K concentrations improved and were within the reference range for the majority of dogs. However, most dogs continued to have a Na/K ratio outside the target range. This shows that normalisation of absolute concentrations of electrolytes are associated

Table 7 Most common abnormal clinical signs reported in each group

Sign	Group Z (N=113)		Group P (N=39)	
	Dogs experiencing this sign n (%)	Probably or possibly related to DOCP* n (%)	Dogs experiencing this sign n (%)	Probably or possibly related to DOCP* n (%)
Polydipsia	55 (48.7)	15 (13.3)	18 (46.2)	6 (15.4)
Polyuria	52 (46.0)	17 (15.0)	17 (43.6)	5 (12.8)
Vomiting	48 (42.5)	4 (3.5)	12 (30.8)	0
Polyphagia	31 (27.4)	2 (1.8)	7 (17.9)	1 (2.6)
Diarrhoea	29 (25.7)	2 (1.8)	9 (23.1)	3 (7.7)
Inappropriate urination	28 (24.8)	9 (8.0)	9 (23.1)	4 (10.3)
Lethargy	24 (21.1)	5 (4.4)	11 (28.2)	1 (2.6)

Group Z: treated with Zycortal.
Group P: treated with Percorten-V.
n (%): number (percentage) of dogs in each group experiencing the stated sign.
*According to the veterinarian's assessment.
.N, total number of dogs in each group administered at least one dose of DOCP.

with successful treatment of PH, whereas normalisation of the Na/K ratio is not. This is not unexpected, for example, if the Na reference range was 140–160 mmol/l, and the K reference range was 3.5–5.8 mmol/l, then only K values ≥ 4.4 mmol/l can mathematically result in a Na/K ratio within the reference range of 27–32. In fact, only K concentrations of 5.0–5.18 will result in a Na/K ratio within the reference range when combined with all possible within-reference range Na concentrations.

Non-inferiority was not demonstrated in the PP analysis at day 180, but was demonstrated in the ITT analysis. This difference in outcomes may have been caused by the high number of dogs (n=27) which were excluded from the PP population due to lack of data collected in the required timeframe at day 180 since the per cent success was higher in group Z than in group P in both the ITT and PP analyses.

The new formulation of DOCP for subcutaneous administration, Zycortal, is safe and effective for use as replacement therapy for mineralocorticoid deficiency in dogs with PH when compared with a positive control, administered intramuscularly.

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