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Effects of desoxycorticosterone pivalate administration on blood pressure in dogs with primary hypoadrenocorticism

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Summary: *A study was designed to evaluate the effects of desoxycorticosterone pivalate (DOCP) on blood pressure in 8 dogs with primary hypoadrenocorticism, and to attempt to identify other factors that might suggest overdosage of the drug. In 4 dogs, primary hypoadrenocorticism had been diagnosed immediately before entry of the dog into the study, and the dogs had not received any mineralocorticoid supplementation. In the other 4 dogs, primary hypoadrenocorticism had been diagnosed 1 to 6 years previously, and dogs were being treated with DOCP at the time of entry into the study. In all 8 dogs, DOCP (2.2 mg/kg of body weight, IM) was administered on days 0, 30, 60, and 90 of the study; each dog was examined on days 0, 30, 60, 75, 90, and 105. At the time of each visit, a medical history was obtained, a complete physical examination and serum biochemical analyses were performed, and body weight and blood pressure were measured. Doppler-shift ultrasonic sphygmomanometry was used to indirectly record systemic systolic and diastolic pressures. None of the dogs developed hypernatremia or hypokalemia or any clinical signs suggestive of hypoadrenocorticism during the study. However, in 6 dogs (3 that had not been previously treated with mineralocorticoids and 3 that had been), there was a significant increase in body weight over the course of the study. Compared with baseline (day 0) arterial blood pressure, neither systolic nor diastolic blood pressure was significantly increased during the study, and all systolic and diastolic blood pressure measurements were within reference ranges at all evaluation times. Results of this study indicate that DOCP fails to increase systolic or diastolic arterial blood pressure when administered at the recommended dosage to dogs with hypoadrenocorticism.*

Desoxycorticosterone pivalate[a] (DOCP), the trimethylacetate ester of naturally occurring desoxycorticosterone, has been used as a long-acting, synthetic mineralocorticoid replacement in human beings and dogs with primary hypoadrenocorticism (Addison's disease).[1-3] Mineralocorticoids exert their effects on the distal convoluted tubules and collecting ducts of the kidneys to cause sodium and chloride retention and potassium wasting, thereby correcting the serum electrolyte imbalances characteristic of primary hypoadrenocorticism (ie, hyponatremia, hypochloremia, and hyperkalemia).[4]

In human beings, hypertension is a common complication of mineralocorticoid excess and a characteristic feature of patients with aldosterone-secreting adrenal tumors (Conn's syndrome).[5-7] Hypertension has also been recorded in human patients with Addison's disease who are treated by administration of high dosages of the mineralocorticoid desoxycorticosterone acetate (DOCA), either the short-acting form administered IM or the pellet form implanted SC.[8] In dogs, hypertension has been experimentally induced by administering a high (5 to 10 times normal) dosage of DOCA daily.[9] However, few studies have been done on the effect of longer-acting mineralocorticoids, such as DOCP, on blood pressure in human patients.[1] The effect of DOCP on blood pressure in clinically normal dogs or in dogs with naturally occurring hypoadrenocorticism has not been investigated, to our knowledge.

The recommended dosage of DOCP (2.2 mg/kg of body weight, administered q 25 d)[3,10] will control serum electrolyte imbalances in almost all dogs with hypoadrenocorticism, and in many dogs, even a lower dose is sufficient. Therefore, we speculated that administration of DOCP at this dosage may induce adverse effects, such as hypertension, in some dogs. The purposes of the study reported here were to evaluate the pressor effect of DOCP in dogs with hypoadrenocorticism, when administered at the recommended dosage of 2.2 mg/kg, IM, at 30-day intervals, and to attempt to identify other indicators that might suggest overdosage of the drug.

Materials and Methods

Case selection—The study population consisted of 8 dogs with naturally occurring primary hypoadrenocorticism. Dogs ranged in age from 2 to 10 years (mean ± SD; 5.4 ± 3.4 years). Five

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breeds were represented. Five dogs were female, and 3 were male; all were neutered. A tentative diagnosis of primary hypoadrenocorticism was made on the basis of clinical and historical signs and results of physical examination and routine clinicopathologic tests (eg, serum electrolytes concentrations). Adrenocortical insufficiency was confirmed in all dogs by finding subnormal baseline serum cortisol concentrations that did not increase after administration of adrenocorticotropic hormone.[11]

Four of the dogs had been treated by IV administration of saline (0.9% NaCl) solution and a glucocorticoid for 2 days while results of adrenocorticotropic hormone stimulation tests were pending, but had not received any mineralocorticoid supplementation. These 4 dogs were entered into the study the day that the diagnosis of adrenocortical insufficiency was confirmed. For the other 4 dogs, hypoadrenocorticism had been diagnosed 1 to 6 years previously, and the dogs had been receiving DOCP at dosages ranging from 1 to 2 mg/kg (mean, 1.5 mg/kg), monthly, at the time of entry into the study; each dog was entered into the study 30 to 35 days after its last DOCP injection. Two of the dogs were concurrently being treated with prednisone (0.2 mg/kg, PO, q 24 h); the dosage of prednisone was not changed throughout the study.

Study design—At time of entry into the study, the following information was obtained for each dog: medical history, body weight, results of a complete physical examination and serum biochemical analyses (including serum sodium, potassium, and urea nitrogen concentrations), and systolic and diastolic blood pressures. The medical history included owners' answers to questions regarding the dog's appetite, vomiting, diarrhea, polyuria, and activity level. Serum biochemical analyses were performed, using an automated analyzer.[b]

After baseline information was obtained, DOCP was administered to each dog at a dosage of 2.2 mg/kg, IM.[3,10] Administration of DOCP was repeated on days 30, 60, and 90, and each dog was reexamined on days 30, 60, 75, 90, and 105. At the time of each visit, the medical history was updated, a complete physical examination was performed, body weight was measured, and serum biochemical analyses and blood pressure measurements were repeated.

Blood pressure determinations—Systemic systolic and diastolic pressures were determined indirectly by use of Doppler-shift ultrasonic sphygmomanometry.[12,13] Doppler signals were recorded with the aid of an ultrasonic Doppler machine,[c] a disposable neonatal-size cuff,[c] and a neonatal ultrasonic pressure transducer.[c] To record the Doppler signals, dogs were held in standing position, and the medial aspect of the hind limb proximal to the hock was shaved. Coupling gel[d] was applied to the shaved area, and the transducer and attached cuff were placed over the cranial tibial artery. The cuff was wrapped snugly around the limb and secured with tape. Blood pressure was measured by inflating the cuff to a pressure 30 to 40 mm of Hg higher than that required to obliterate the pulse. The cuff was then slowly deflated, and systolic blood pressure was recorded as the cuff pressure at which blood flow sounds first became audible (phase I). As pressure in the cuff was further decreased, the intensity of the sound usually increased (phases II and III). Diastolic blood pressure was recorded as cuff pressure at which intensity of blood flow sounds abruptly decreased and blood flow sounds became muffled (phase IV).[13]

Excitement and stress were minimized by performing blood pressure measurements in a quiet room with the least amount of restraint possible. Each dog was comforted by its owner for approximately 5 minutes with cuff in place. Owners then left the room, and blood pressures were measured 5 times over a 5- to 10-minute interval and were averaged.

To establish reference ranges for systolic and diastolic blood pressures, we measured arterial blood pressure in 12 clinically normal dogs, using the same technique. These 12 dogs were pets owned by employees of the hospital. The dogs ranged in age from 1 to 9 years (mean ± SD; 4.3 ± 2.6 years). Six dogs were male, and 6 were female. Six breeds were represented. All dogs were determined to be healthy on the basis of history and physical examination. In these dogs, mean (± SD) systolic and diastolic blood pressures were 142.5 ± 7.9 and 85.8 ± 5.2 mm of Hg, respectively.

Statistical analysis—Results are given as mean ± SD. Because blood pressure data obtained from the clinically normal dogs fit criteria for being gaussian in distribution, reference ranges for systolic and diastolic pressures were considered to be the intervals bounded by the mean ± 2 times the SD.[14]

For the dogs with hypoadrenocorticism, baseline blood pressures and body weights were compared with pressures and weights obtained following administration of DOCP, and baseline (day 0) serum concentrations of sodium, potassium, and urea nitrogen were compared with concentrations measured on days 30, 60, 75, 90, and 105 by use of ANOVA for repeated measures.[15] Single-factor ANOVA was used to compare mean systolic and mean diastolic blood pressures of the 8 dogs with primary hypoadrenocorticism with mean blood pressures of the clinically normal dogs.[14] For all statistical analyses, a value of $P \leq 0.05$ was considered significant.

Results

All of the dogs responded well to treatment with DOCP, and none of the dogs developed any serum sodium or potassium concentration abnormalities (ie, hypernatremia or hypokalemia) or any

Table 1—Serum concentrations of sodium and potassium in 8 dogs with hypoadrenocorticism before (day 0) and after treatment with desoxycorticosterone pivalate (2.2 mg/kg/mo, IM)

Time (d)	Serum sodium concentration (mEq/L)	Serum potassium concentration (mEq/L)
0	143±5.2 (135 to 150)	4.5±0.5 (3.8 to 5.5)
30	145±5.1 (139 to 152)	4.6±0.9 (3.5 to 5.4)
60	146±2.9 (142 to 151)	4.6±0.5 (3.8 to 5.2)
75	146±4.6 (140 to 154)	4.8±0.8 (3.5 to 5.2)
90	146±3.3 (140 to 150)	4.7±0.6 (3.7 to 5.4)
105	147±2.5 (142 to 149)	4.5±0.4 (3.8 to 5.0)
Reference range	139 to 154	3.5 to 5.5

Results are given as mean ± SD. Numbers in parentheses indicate range.

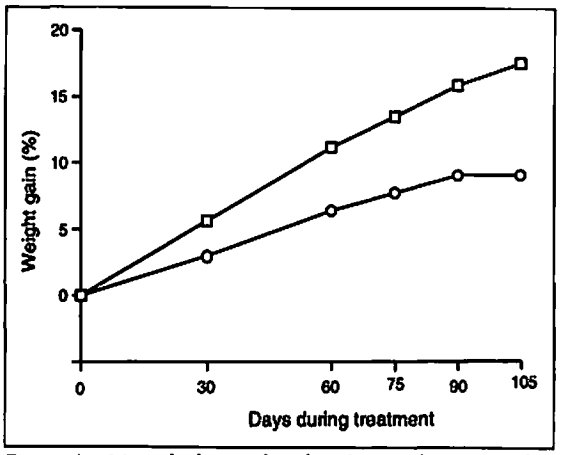

Figure 1—Mean body weight of 8 dogs with primary hypoadrenocorticism before (day 0) and 30, 60, 75, 90, and 105 days after initiation of treatment with desoxycorticosterone pivalate (DOCP), administered at a dosage of 2.2 mg/kg/mo, IM. Four dogs had not received any prior mineralocorticoid treatment (—□—), and the remaining 4 had been previously treated with DOCP (1 to 2 mg/kg/mo) at the time of entry into the study (—○—).

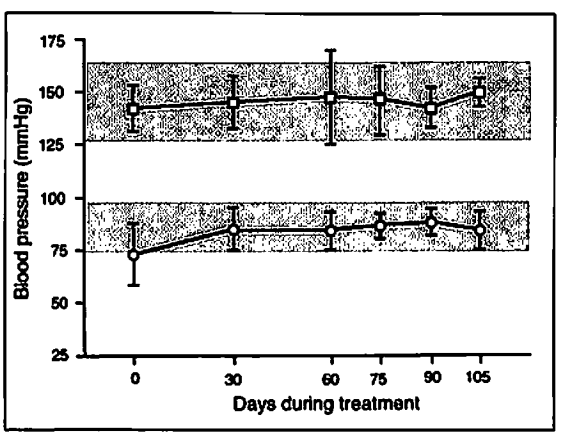

Figure 2—Mean systolic (—□—) and diastolic (—○—) blood pressures of 8 dogs with primary hypoadrenocorticism before (day 0) and 30, 60, 75, 90, and 105 days after initiation of treatment with DOCP (2.2 mg/kg/mo, IM). Bars represent SD; shaded areas indicate the reference ranges for systolic and diastolic blood pressure.

clinical signs suggestive of hypoadrenocorticism during the 105-day treatment period. Compared with baseline (day 0) concentrations, there was no significant change in mean serum concentration of sodium or potassium during the study (Table 1).

There was a significant ($P < 0.05$) increase in mean body weight over the course of the study. Three of the 4 dogs that had previously been treated with DOCP gained weight (mean weight gain, 8.9%) without any changes in eating habits, exercise patterns, or glucocorticoid administration (Fig 1). These 3 dogs had previously received DOCP at a dosage (ie, 1.0 to 1.6 mg/kg/mo) less than that used during the study. Three of the 4 dogs that had not received any previous mineralocorticoid treatment also gained weight (mean weight gain, 17.3%).

Compared with baseline (day 0) arterial blood pressures, neither mean systolic nor mean diastolic blood pressure was significantly increased during the study (Fig 2). Blood pressures of the 4 dogs that had not received any mineralocorticoid supplementation prior to entry into the study were not significantly different from those of the 4 dogs that had been previously treated with DOCP at any time during the treatment period. In addition, at all times during the study, mean systolic and diastolic arterial blood pressures of the 8 dogs with hypoadrenocorticism were not significantly different from blood pressures of the clinically normal dogs.

Discussion

The first study reporting the successful use of DOCP in a dog with hypoadrenocorticism was published in 1971.[2] Since then, DOCP has been shown to be an effective alternative to fludrocortisone acetate, the other replacement mineralocorticoid available for management of hypoadrenocorticism in dogs.[3,10,16] This is particularly true for owners who are unable to comply with daily or twice daily administration required with fludrocortisone, and for dogs that, because of the glucocorticoid properties of fludrocortisone, develop clinical signs of glucocorticoid excess during treatment with the drug.[17]

However, one of the major effects of all mineralocorticoids is to increase reabsorption of sodium from the renal tubule. Because extracellular water follows the movement of sodium, increased reabsorption of sodium will directly increase total extracellular fluid volume and may, thereby, indirectly increase blood volume and blood pressure, resulting in hypertension.[4] Hypertension is common in people with naturally occurring hyperaldosteronism (ie, in people with nodular hyperplasia of the zona glomerulosa of the adrenal cortex or aldosterone-producing adrenal tumors),[5-7] and has been reported in people with Addison's disease who are treated with excessive dosages of the short-acting injectable mineralocorticoid DOCA.[18]

Hypertension has also been related to excessive dosages of mineralocorticoid in rats and dogs, but only under unnatural conditions. In 1 study, hypertension was induced in rats by performing unilateral nephrectomy, providing drinking water

high in sodium chloride content, and administering massive dosages of DOCA[19] and, in another study, by feeding a high salt diet and administering high dosages of DOCP.[20] Similarly, hypertension was induced in dogs by combining unilateral nephrectomy with administration of an overdosage of DOCA for a 60-day period.[21] However, administration of DOCA alone (15 mg/kg/d, SC, for 14 days) to dogs receiving a normal salt intake did not cause severe hypertension, even though it did increase blood pressure.[22]

Our study failed to demonstrate a significant elevation in systolic or diastolic arterial blood pressures when dogs with hypoadrenocorticism were treated with the recommended dosage of DOCP (2.2 mg/kg/mo) for 3 months. Three of the 4 dogs that underwent treatment with DOCP before the study had been maintained on dosages considerably below the recommended dosage of 2.2 mg/kg, and historically, most dogs with hypoadrenocorticism can be maintained on dosages as low as 1.4 to 1.8 mg/kg/mo.[17] Therefore, it is reasonable to assume that most of the dogs in our study were receiving a dosage in excess of their need. In light of the difficulties involved in the experimental induction of hypertension solely by overdosage of DOCA,[22] our findings would seem to suggest that there are regulatory mechanisms that prevent mineralocorticoid excess from causing chronic volume overload and secondary hypertension. In support of that, there have been multiple reports describing the role of atrial natriuretic peptide in the prevention of disease-induced plasma volume overload.[22-24]

The change in body weight seen in most dogs in this study was of clinical interest. Weight loss is a characteristic clinical sign in dogs with untreated hypoadrenocorticism, and one would expect that such dogs would regain the lost weight after institution of appropriate replacement treatment. This probably accounted for at least some of the weight gain recorded in these dogs. However, 3 of the 4 dogs that had been receiving DOCP prior to entry into the study and in which clinical signs of hypoadrenocorticism had been well-controlled also gained weight when their monthly dosage of DOCP was increased for the purposes of this study. In many species, including dogs, it is well-recognized that chronic exposure to endogenous or exogenous mineralocorticoid excess will result in a transient period of positive sodium balance, accompanied by an expansion of the extracellular fluid volume. This expansion is evident clinically as an increase in body weight and is maintained even after sodium balance is restored.[24] In a study of human patients with Addison's disease, for instance, subjects consistently gained weight during the first 2 to 3 weeks after each monthly injection of DOCP, then gradually lost weight over the next 1 to 2 weeks.[1] As with the dogs of this study, none of these human patients developed peripheral or pulmonary edema or an excessive rise in blood pressure. Therefore, although we did not determine extracellular volume in this study, the significant weight gain suggests that DOCP, when administered at a dosage greater than that necessary to maintain normal electrolyte concentrations, may result in extracellular volume retention, at least in some dogs. In dogs treated with DOCP that gain excessive weight, reduction of the dosage of DOCP should be considered, but only if normal serum concentrations of sodium and potassium are maintained when the dogs receive the lower dosage.

[a]Percorten-V, CIBA-GEIGY Animal Health, Greensboro, NC.
[b]Hitachi 717 automatic analyzer, Boehringer Mannheim Co, Indianapolis, Ind.
[c]Kontron Medical Instruments, Everett, Mass.
[d]Gelisonde 8098, Hoffmann-LaRoche Inc, Crabury, NJ.

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