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Retrospective Study of Desoxycorticosterone Pivalate (DOCP) in Hypoadrenocorticism Dog

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Abstract : Hypoadrenocorticism results from the deficient adrenal gland production of glucocorticoids or mineralocorticoids. Fludrocortisone have been used for the management of hypoadrenocorticism in dogs. But desoxycorticosterone pivalate (DOCP) have been administered for management of hypoadrenocorticism in dogs since several years because of the equivalent effect of fludrocortisone, and lessening of owner and patient's effort. The therapy of DOCP was evaluated in 14 dogs diagnosed with hypoadrenocorticism based on clinical signs, an electrolyte imbalance, and the results of an adrenocorticotropic hormone stimulation test. DOCP was administered at 25-day intervals at an initial dose of 2.2 mg/kg. The dogs were monitored for clinical signs and serum electrolyte, blood urea nitrogen, and creatinine concentrations every 25 days. Fludrocortisone was an effective treatment in dogs overall; however, a change to DOCP was necessary in 7 dogs because of adverse effects or poor responses. Another 7 dogs were treated with DOCP from the first time. A total of 14 dogs were treated with DOCP. Clinical signs and electrolyte imbalance resolved completely in 12 dogs. However, mild clinical signs, such as shivering, remained in 2 dogs, and 4 dogs required regular supplementation with prednisone. Improvements in clinical signs and electrolyte imbalance were significantly better after treatment with DOCP than with fludrocortisone. The results suggest that DOCP may be a better choice than fludrocortisone for the management of hypoadrenocorticism in dogs.

Key words **:** hypoadrenocorticism, DOCP, dogs, fludrocortisone.

Introduction

Hypoadrenocorticism results from the deficient production of glucocorticoids or mineralocorticoids in the adrenal gland. A lack of mineralocorticoids causes hyponatremia and hyperkalemia. Hyponatremia causes a decrease in circulating blood volume, prerenal azotemia, hypotension, and other physiological conditions. In addition, hyperkalemia induces myocardial toxicity (6). Hypoadrenocorticism seems to be a disease of young to middle-aged dogs ranging in age between 3 months and 14 years (median age: 4 years). The clinical signs of dogs with hypoadrenocorticism are vomiting, diarrhea, weight loss, lethargy, dehydration, shivering, polydipsia, polyuria, anorexia, among others. These signs may wax and wane or be acute (1,3,6).

The diagnosis of hypoadrenocorticism is based on medical history, clinical signs, and laboratory findings, such as hyperkalemia, hyponatremia, and low sodium: potassium ratios. A definitive diagnosis of hypoadrenocorticism can be made with an adrenocorticotropic hormone (ACTH) stimulation test (1,4-6).

Mineralocorticoid supplementation is necessary to maintain an electrolyte balance in hypoadrenocorticism that is caused by destruction of the adrenal cortex. Initial emergency therapies to correct hypovolemia, electrolyte abnormalities, and hypoglycemia include fluid therapy and supplementation with glucose, dexamethasone, and prednisone (8). To manage hypoadrenocorticism, treatment is directed at the physiologic replacement of the deficient mineralocorticoids by using fludrocortisone (Florinef®; ER Squibb & Sons, Inc, USA) or desoxycorticosterone pivalate (DOCP) (Percorten-V®; Novartis Animal Health US, Inc, USA). Prednisone or prednisolone can be used for the supplementation of glucocorticoids (4). DOCP, the trimethylacetate ester of desoxycorticosterone, is a long-acting repositol synthetic mineralocorticoid but has no glucocorticoid activity; therefore, prednisone should be supplemented at physiologic doses. DOCP, which is administered intramuscularly every 25 days, is more convenient than the daily oral administration of fludrocortisone.

However, only one case of treatment with DOCP against canine hypoadrenocorticism uncontrolled with fludrocortisones (9) was reported until now in Korea but the retrospective study of treating with DOCP in hypoadrenocorticism has not been reported in domestic veterinary medicine. This study retrospectively evaluated the efficacy and adverse effects of long-term therapy with DOCP in 14 dogs with hypoadrenocorticism.

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Materials and Methods

This investigation was conducted in 14 dogs with hypoadrenocorticism at the Seoul National University Hospital for Animals from June 2004 to August 2010. The age of the 14 dogs ranged from 2 to 15 years (mean age: 7 y). Most of the dogs (9 cases) with hypoadrenocorticism were intact females, 4 dogs were castrated males, and 1 dog was a spayed female. Five dogs were Maltese and 3 dogs were Cocker Spaniels. The diagnosis of hypoadrenocorticism was based on a medical history, a complete physical examination, serum biochemical analysis, complete blood counts, abdominal radiography, and ultrasonography. Depending on the test results, Hypoadrenocorticism was confirmed by ACTH stimulation test. An ACTH stimulation test involves the administration of 5 μg/kg of synthetic ACTH (tetracosactide acetate, Synacten®; Alliance Pharmaceuticals Ltd, England) intravenously after obtaining an initial blood sample. A second blood sample was drawn 1 hour after the administration of ACTH for the measurement of cortisol concentrations at the Neodin Veterinary Lab (Seoul Korea). The cortisol concentrations were measured by the electrochemiluminescence immunoassay. Hypoadrenocorticism was defined as a cortisol concentration less than 2 μg/dl (3,6).

Before hypoadrenocorticism was diagnosed, dogs with an electrolyte imbalance and dehydration were treated with isotonic fluids (i.e., 0.9% saline or Ringer's solution) intravenously. In some cases, symptomatic treatment to improve clinical signs such as vomiting, diarrhea, and melena was indicated. In 7 of the 14 dogs with hypoadrenocorticism, fludrocortisone was initially used for mineralocorticoid replacement, and then 2.2 mg/kg of DOCP was injected intramuscularly because of a poor response to fludrocortisone. The remaining 7 dogs with hypoadrenocorticism were initially administrated with DOCP (2.2 mg/kg) every 25 days intramuscularly or subcutaneously. Electrolyte levels were measured 12 days after DOCP administration to monitor the peak effect of this drug for dose adjustments and evaluation of therapeutic efficacy. If potassium level had increased (> 5.0 mEq/L) and the sodium level had decreased (< 141 mEq/L) at that time, the dose was increased by 10% to 25% at the next administration. If the potassium level had decreased (< 3.8 mEq/L) and the sodium level had increased (> 152 mEq/L), the dose was decreased by 10% to 25%. If the serum electrolyte level was normal, the dose was maintained. Electrolyte levels were remeasured after 25 days to monitor the duration of efficacy, and the injection interval was decreased by 1 to 2 days if high potassium and/or low sodium concentrations were determined at that time. Unlike fludrocortisone, DOCP has no corticosteroid activity. Therefore, 0.22 mg/kg of prednisone was prescribed only during illness with a non-adrenal related disease and stress. It was rechecked at 25 day intervals to determine the presence or absence of clinical signs, electrolyte imbalance and azotemia.

Results

All 14 dogs had symptoms of anorexia, 11 dogs experienced vomiting, 5 dogs experienced shivering, and 4 dogs experienced melena. Iatrogenic hypoadrenocorticism occurred in 1 of the 14 dogs diagnosed with hyperadrenocorticism that was being treated with mitotane (Table 1).

On physical examination, all of the dogs were found to have dehydration (5-8%). On the basis of laboratory results, 13 of 14

Table 1. Signalment of 14 dogs with hypoadrenocorticism

Case No.	Age (years)	Breed	Gender	Clinical signs
1	15	Shih Tzu	F	Vomiting, anorexia, melena
2	4	Cocker Spaniel	F	Vomiting, anorexia, shivering, melena
3	3	Cocker Spaniel	F	Vomiting, anorexia, shivering
4	3	Cocker Spaniel	F	Vomiting, anorexia, shivering, melena
5	3	Maltese	MC	Anorexia, body weight loss
6	15	Yorkshire Terrier	F	Vomiting, anorexia
7	8	Yorkshire Terrier	F	Anorexia, shivering
8	4	Maltese	MC	Vomiting, anorexia
9	10	Mixed	MC	Vomiting, anorexia
10	2	Maltese	FS	Anorexia
11	9	Shih Tzu	F	Vomiting, anorexia
12	8	Mixed	MC	Vomiting, anorexia, melena
13	8	Maltese	F	Vomiting, anorexia, shivering, seizure
14	7	Maltese	F	Vomiting, anorexia, hypoglycemia

F: female, FS: spayed female, MC: castrated male

dogs had both hyponatremia and hyperkalemia; the remaining 1 dog had hyperkalemia without hyponatremia. The average sodium: potassium ratio was 18.95 ± 1.038:1 (range: 13.5~25.47:1) (Table 2). For the 9 of 14 dogs with azotemia, abdominal ultrasonography was performed to rule out other disease; the bilateral adrenal gland was shown to have decreased in size in 3 of these dogs. Both serum pre-ACTH and post-ACTH cortisol concentrations through an ACTH stimulation test were less than 2 μg/dl in all 14 dogs. All 14 dogs were diagnosed hypoadrenocorticism on the basis of these findings (Table 2).

In 7 of 14 dogs with hypoadrenocorticism, fludrocortisone was initially used for mineralocorticoid replacement. However, because of adverse effects such as polydipsia/polyuria (PU/PD, n = 1) and poor improvement continuing electrolyte imbalance (n = 6), the drug was switched to DOCP. For the 4 of 6 dogs that showed a poor response to fludrocortisone, the dose of fludrocortisone was continuously increased by 0.062 ± 0.02 mg/kg/day. In the 7 dogs that were initially treated with DOCP, prednisone was prescribed when the dogs were faced with stressful situations. Electrolyte levels were evaluated 12 and 25 days after DOCP administration. Dose adjustments of DOCP and the interval of administration were determined on the basis of these results and the average injection interval of DOCP was 26.42 ± 0.41 days (range: 24~28 days).

In 12 dogs, the maintenance dose of DOCP required was 2.2 mg/kg-the same as the initial dose. This dose was increased to 2.42 mg/kg (by 10%) in two dogs that continued to have an electrolyte imbalance. The average sodium: potassium ratio was 18.95 ± 1.038:1 (range: 13.5~25.47:1) prior to treatment, which increased to 22.52 ± 0.79:1 (range: 18.8~25.5:1) after the administration of fludrocortisone. The average sodium: potassium ratio was 31.39 ± 0.85:1 (range: 27.8~36.34:1) after DOCP injection (Table 2).

Discussion

This study showed that the dose of fludrocortisone was continuously increased in some dogs because of a poor response. However, the effectiveness of such treatment was not sufficient to resolve the electrolyte imbalance and clinical signs. Moreover, adverse effects related to excess glucocorticoids, such as PU/PD and polyphagia, were observed. In a retrospective study conducted in 1997 by Kintzer and Peterson, 62 of 200 dogs treated with fludrocortisone for hypoadrenocorticism showed clinical signs of iatrogenic hyperadrenocorticism, such as PU/PD, polyphagia, weight gain, and hair loss (2). In Korea, one case of adverse effects related to fludrocortisones was reported in a dog. In that case, fludrocortisone was switched to DOCP for mineralocorticoid replacement, which was effective at resolving the side effects and was not associated with

Table 2. The results of an ACTH stimulation test, serum sodium: potassium ratio before treatment, after treatment with fludrocortisones and DOCP, survival time from diagnosis to the time of death or last follow-up in 14 dogs with hypoadrenocorticism

Case No.	Pre-ACTH cortisol conc. (μg/dl)	Post-ACTH cortisol conc. (μg/dl)	Na:K ratio Pre-treatment	Na:K ratio Fludrocortisone administration[1]	Na:K ratio DOCP administration[2]	Survival time from diagnosis (days)
1	0.01	0.12	24.2:1	22.5:1	32:1	672 (death)
2	0.16	0.15	14.8:1	23.1:1	29:1	2284
3	0.01	0.01	17.9:1	23.3:1	30.1:1	2001 (death)
4	0.01	0.01	15.9:1	23.4:1	32.7:1	1700
5	0.01	0.01	18:1	25.5:1	32.7:1	1418
6	0.1	0.18	13.5:1	18.8:1	24.7:1	217 (death)
7	0.4	0.4	18.5:1	-	27.8:1	268
8	1.0	1.0	13.5:1	-	33.95:1	561
9	1.0	1.0	25.47:1	-	30:1	455
10	1.2	0.8	21.07:1	21.1:1	31.2:1	1128
11	1.0	1.0	18.2:1	-	29:1	256
12	1.0	1.0	21.86:1	-	35:1	226
13	1.0	1.0	21.79:1	-	36.34:1	181
14	1.0	1.0	12.66:1	-	35:1	179

[1)]The sodium: potassium ratio measured before changing to DOCP.
[2)]The sodium: potassium ratio measured 25days after first DOCP administration.

adverse effects, such as PU/PD and polyphagia. The reason for the difference between fludrocortisone and DOCP is probably the result of glucocorticoid activity (9).

Despite the increased dose of fludrocortisone, azotemia and electrolyte imbalance did not improve in some cases. This lack of improvement likely means that fludrocortisone is insufficient for the management of hypoadrenocorticism. In a retrospective study conducted in 1997, 7 of 200 dogs treated with fludrocortisone for hypoadrenocorticism showed poor responses; therefore, mineralocorticoid replacement was switched to DOCP (2). In our study, fludrocortisone was replaced with DOCP in 7 dogs for the same reasons.

In 6 dogs treated with an initial dose of 0.02 mg/kg/day of fludrocortisones, the dose of fludrocortisones was increased because azotemia and electrolyte imbalance remained unresolved; the final dose averaged 0.062 ± 0.02 mg/kg/day. But azotemia and electrolyte imbalance were continuing. Consequently, the medication was switched to DOCP, after which the clinical signs related to uncontrolled hypoadrenocorticism and electrolyte imbalance disappeared. On the basis of the findings, DOCP seems to be more effective than fludrocortisone at resolving clinical signs and electrolyte imbalance in dogs with hypoadrenocorticism.

However, mild electrolyte imbalance and clinical signs, such as shivering and partial anorexia, remained in 2 cases after the switch to DOCP. This result indicates that DOCP does not sufficiently manage hypoadrenocorticism in some cases. However, these symptoms improved with temporary prednisone treatment and fluid therapy. The temporary administration of prednisone is effective at controlling symptoms caused by stressful situations. Furthermore, intermittent administration of prednisone did not cause adverse effects. Thus, dog owners should administer prednisone to their dogs under stressful situations. Otherwise, clinical signs related to glucocorticoid deficiency, such as partial anorexia, can occur. Prednisone was administered periodically to 4 of the 14 dogs in the present study at intervals of 2 to 7 days. When prednisone administration was discontinued in these 4 dogs, depression and partial anorexia were identified. Although many hypoadrenocorticism patients did not require prednisone, only DOCP treatment without prednisone may be unable to completely resolve the clinical signs.

Eleven of the 14 dogs in the current study are still alive with a good condition and 3 dogs (case 1, 3, and 6) died. It was assumed that the death of them was caused by other diseases except hypoadrenocorticism. One of died dogs was supposed to lead to death due to transitional cell carcinoma after the survival time of 217 days. Another one was died due to pulmonary edema caused by heart failure and its survival time was 672 days. The other one died from nongenerative anemia and chronic kidney disease with the 2001 days' survival time (Table 2).

Conclusion

In the current survey, 14 dogs with a diagnosis of hypoadrenocorticism were managed with fludrocortisone or DOCP. Improvements in clinical signs and electrolyte imbalance were significantly better after treatment with DOCP than with fludrocortisone. Thus, DOCP injection may be more effective than prescribing fludrocortisone. However, some patients treated with DOCP required the periodic administration of prednisone. DOCP treatment is more convenient than fludrocortisone because only one injection is needed every 25 days to manage hypoadrenocorticism, and dog owner satisfaction was greater with DOCP than with fludrocortisone in our study. On the basis of the current results, treatment with DOCP is superior to that with fludrocortisone for the management of hypoadrenocorticism.

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부신피질기능저하증 개를 DOCP로 치료한 후향적 연구

고예린 · 서경원 · 안진옥 · 채지상 · 박종우 · 방동하 · 채준석 · 윤화영[1] · 황철용[1]

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요 약 : 부신피질기능저하증은 부신에서 생산되는 글루코코르티코이드와 미네랄로코르티코이드의 결핍으로 발생한다. 개에서 부신피질기능저하증을 관리하기 위해 fludrocortisone이 사용되어왔다. 그러나 desoxycorticosterone pivalate의 경우 fludrocortisone과 대등한 효과와 보호자와 환자에게 적은 부담을 주기 때문에 최근 몇 년간 부신피질기능저하증 개의 관리를 위해 사용되었다. 임상증상, 전해질불균형, adrenocorticotropic hormone stimulation test를 통하여 부신피질기능저하증으로 진단된 14마리의 개에서 DOCP의 효과를 분석하였다. DOCP의 초기용량은 2.2 mg/kg 으로 사용되었으며 25일 간격으로 근육 또는 피하로 주사되었다. DOCP의 효능을 보기 위해 25일 간격으로 임상증상, 혈청 전해질 수치, 혈청 요소질소, 크레아티닌 수치를 모니터링 하였다. Fludrocortisones은 개에서 효과적인 치료법이지만 부작용과 불충분한 반응으로 7마리의 개에서 DOCP로의 전환이 필요하였다. 7마리의 개는 처음부터 DOCP가 투약되어 총 14마리의 개가 DOCP로 관리 받았다. 12마리의 개에서 임상증상, 전해질 불균형이 완전히 해소되었으나 2마리의 개에서는 몸 떨림과 같은 약간의 임상증상이 여전히 남아있었다. 4마리의 개는 프레드니손의 정기적 투여가 필요하였다. 이러한 결과를 종합해 보면, fludrocortisone과 비교하여 DOCP가 임상증상과 전해질불균형의 개선에 훨씬 효과적이었으며 이 결과는 부신피질기능저하증 개에서 DOCP가 더 좋은 치료법임을 제시해준다.

주요어 : 개, 부신피질기능저하증, fludrocortisone, DOCP