Iatrogenic Hyperadrenocorticism in 28 Dogs

Twenty-eight dogs with iatrogenic hyperadrenocorticism were studied. The most common clinical signs were cutaneous lesions (27/28), polydipsia (21/28), polyuria (19/28), and lethargy (16/28). The most predominant findings on biochemical profile were elevated alkaline phosphatase (ALP, 15/28) and alanine transferase (ALT, 14/28); hypercholesterolemia (14/28); elevated aspartate transferase (AST, 12/28); and elevated triglycerides (12/18). Baseline cortisol levels of all 28 dogs were at the lower end of the reference range and exhibited suppressed or no response to adrenocorticotropic hormone (ACTH) stimulation. The mean time for each dog to show initial improvement of clinical signs after corticosteroid withdrawal was six weeks, with another mean time of 12 weeks to demonstrate complete remission.

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Introduction

Iatrogenic hyperadrenocorticism (IHAC) results from excessive administration of corticosteroids.[1–4] This condition can be induced by topical, parenteral, or oral medications containing corticosteroids.[5–7] As in spontaneous hyperadrenocorticism, the most common clinical signs for IHAC are polyuria and polydipsia, together with cutaneous and conformational abnormalities.[1–4] The development of signs of glucocorticoid excess depends on the dosage and duration of the exposure.[3] The diagnosis of IHAC is based on a history of corticosteroid administration, clinical and physical findings consistent with hyperadrenocorticism, and evaluation of the pituitary-adrenocortical axis.[1–7]

Adrenocorticotropic hormone (ACTH) release is easily suppressed by exogenous corticosteroids due to feedback mechanisms of the hypothalamic-pituitary-adrenocortical (HPA) axis.[5] This results in failure of the adrenal gland to respond to ACTH administration.[5,8–12] In the presence of clinical signs of hyperadrenocorticism, results of diagnostic tests to assess the HPA axis show differentiation between IHAC and secondary iatrogenic or spontaneous hypoadrenocorticism.[1–4]

The purpose of this study is to report the clinical manifestations of IHAC in 28 dogs.

Materials and Methods

Twenty-eight dogs with cutaneous abnormalities and progressive illness, which were referred to the National Taiwan University Animal Hospital (NTUAH) for further investigation, were enrolled in this study. Breeds represented included six Maltese terriers; five Pomeranians; four mongrels; three each of Chihuahuas, miniature pinschers, and shih tzu; and one each of rough collie, miniature poodle, Shiba Inu, and West Highland white terrier. There were 18 intact males, nine intact females, and one spayed female. The mean age was 5.0±2.8 years and ranged from 10 months to 14 years. The mean body weight was 5.9 kg and ranged from 1.6 to 14.5 kg.

The diagnosis of IHAC in the present study was based on a history of treatment with oral, parenteral, or topical corticosteroids (for various skin disorders) for more than one month prior to referral to NTUAH; clinical

Table 1

Breeds of Dogs Affected With Iatrogenic Hyperadrenocorticism as Well as Route, Type, Dose, and Frequency of Glucocorticoid Used

Case / Breed	Route*	Glucocorticoids†	Frequency‡
Chihuahua	Oral	P	BID
West Highland white terrier	Oral	Unknown	BID
Shihba Inu	Oral	Unknown	BID
	Otic	T	BID
Chihuahua	Oral	P	BID
	Otic	H	BID
Pomeranian	Oral	Unknown	BID
	Topical	H	BID
Maltese	Parenteral	Unknown	SID
Mongrel	Parenteral	T	SID
Mongrel	Parenteral	T	SID
Pomeranian	Oral	P	BID
	Parenteral	T	Q3D
Shih tzu	Oral	Unknown	BID
	Parenteral	D	Q3D
Pomeranian	Oral	Unknown	BID
	Parenteral	T	Q3D
Shih tzu	Oral	Unknown	BID
	Parenteral	T	Q3D
Mongrel	Oral	Unknown	BID
	Parenteral	D	Q3D
Miniature poodle	Oral	P	BID
	Parenteral	T	QW
Mongrel	Oral	Unknown	BID
	Parenteral	T	Q3D
Maltese	Oral	Unknown	BID
	Parenteral	T	QW
Pomeranian	Oral	Unknown	BID
	Parenteral	D	Q3D
Maltese	Oral	Unknown	BID
	Parenteral	D	Q3D
Maltese	Oral	Unknown	BID
	Parenteral	D	QW
	Otic	H	BID
	Topical	H	BID
Miniature pinscher	Oral	Unknown	BID
	Parenteral	T	QW
	Otic	H	BID
	Topical	B	BID
Rough collie	Oral	Unknown	BID
	Parenteral	T	QW
	Topical	H	BID
Miniature pinscher	Topical	B	BID
Chihuahua	Topical	B	TID
Miniature pinscher	Topical	B	QID
Maltese	Topical	B	TID
Pomeranian	Otic	T	TID
Maltese	Otic	T	TID
Shih tzu	Opthalmic	D	BID

* Parenteral=subcutaneously in all dogs

† P=prednisolone; T=triamcinolone; H=hydrocortisone; D=dexamethasone; B=betamethasone

‡ BID=twice daily; SID=once daily; Q3D=every three days; QW=every week; TID=three times daily; QID=four times daily

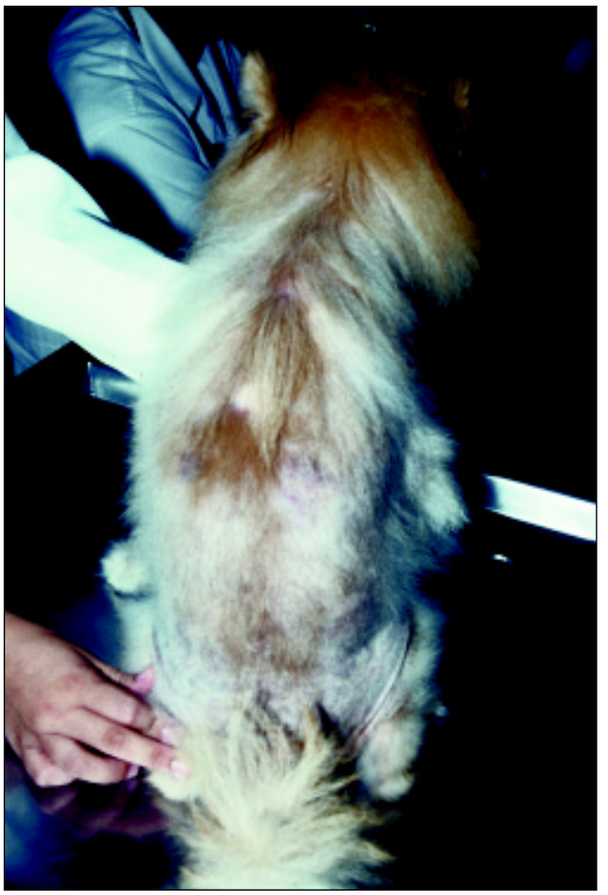

Figure 1—Excessive bilateral hair loss on truncal regions, as well as posterior and lateral aspect of the thighs in a dog with iatrogenic hyperadrenocorticism.

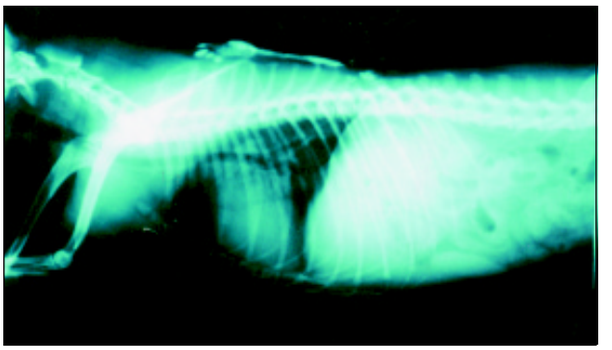

Figure 2—Lateral survey radiograph demonstrating the formation of calcinosis cutis over the spinous processes of the thoracic vertebrae in a dog with iatrogenic hyperadrenocorticism. This is the same dog as seen in Figure 1.

Figure 3—As the iatrogenic hyperadrenocorticism progressed, alopecia often extended from the head to the tail in affected dogs.

and cutaneous abnormalities which were consistent with canine hyperadrenocorticism; and a suppressed cortisol response to ACTH administration. The duration of treatment for the various skin disorders, administration routes, clinical presentation, and findings on physical examinations were recorded. For each case, a complete blood cell count (CBC),[a] a serum biochemical profile,[b] and an ACTH stimulation test were also carried out at initial consultation. The ACTH stimulation test was performed using synthetic ACTH[c] at 0.25 mg intramuscularly. Samples for serum cortisol determination were collected prior to and one hour after ACTH administration. The cortisol levels were measured using a validated radioimmunoassay.[d]

The blood sodium to potassium ratios were monitored every two to four weeks, after IHAC was diagnosed and throughout the period of IHAC resolution.

Results

The mean period of treatment for skin disorders prior to referral to NTUAH was 9.4 months and ranged from one to 36 months. Among these 28 dogs, two were medicated orally; three were medicated both orally and topically; three were medicated parenterally only; 13 were medicated both orally and parenterally; and seven were medicated only topically (skin, ear, or eye) during the treatment period. Routes of medicine administration and frequency are summarized in Table 1.

Among these 28 dogs, 27 showed skin lesions at the time of referral. The most apparent clinical abnormalities were cutaneous signs, including localized or generalized thinning of the hair coat or excessive hair loss (23/28) and localized or generalized alopecia (19/28). Excessive hair loss or alopecia was bilateral and involved mainly the frontal and temporal regions of the head, pinna, truncal regions, and the medial and posterior aspects of the thighs [Figure 1]. Seventeen dogs (17/28) suffered from localized or generalized pyoderma, and nine dogs (9/28) had developed cutaneous hyperpigmentation. Calcinosis cutis was found in four dogs (4/28) [Figure 2]. Thirteen dogs medicated both orally and parentally were found to have severe cutaneous lesions, including generalized papules, pustules, crusts, scale,

Table 2

Clinical Findings on Physical Examinations of 28 Dogs With Iatrogenic Hyperadrenocorticism

Clinical Findings	No. of Dogs
Cutaneous lesions	
Localized or generalized thin coat	23
Localized or generalized alopecia	19
Localized or generalized pyoderma	17
Hyperpigmentation	9
Calcinosis cutis	4
Chief complaints on presentation	
Polydipsia	21
Polyuria	19
Lethargy	16
Polyphagia/ravenous appetite	15
Physical examination findings	
Hepatomegaly	15
Pot-belly	13
Obese	8
Muscular atrophy	8

alopecia, and hyperpigmentation. The lesions usually developed from the head initially and then extended to the tail [Figure 3]. However, seven dogs medicated topically were found to have mild cutaneous lesions, which were characterized by bilateral and localized alopecia involving the temporal regions, neck, forearms, and medial and posterior aspects of the thighs [Figure 4].

Apart from cutaneous abnormalities, polydipsia (21/28) and polyuria (19/28) were most commonly reported by the owners. More than 50% of these dogs (16/28) were lethargic at the time of referral. Fifteen dogs (15/28) were polyphagic or had ravenous appetites.

Hepatomegaly (15/28) was the most common finding on physical examination. Of these 15 dogs, 13 had a pot-bellied appearance and eight were obese. Muscular atrophy of both thighs and temporal regions was found in eight dogs (8/28).

The clinical findings and results of physical examinations of these 28 dogs are summarized in Table 2.

Eosinopenia (18/28) was the most predominant finding on hematological profiles [Tables 3, 4]. Remaining hematological parameters were unremarkable [Table 3]. The most predominant findings on biochemical profiles were elevations of ALP (15/28), ALT (14/28), cholesterol (14/28), AST (12/28), and triglycerides (12/28) [Tables 3, 4]. Hyperglycemia was also found in 10 dogs (10/28) [Tables 3, 4]. The remaining biochemical parameters were all within the reference ranges [Table 3].

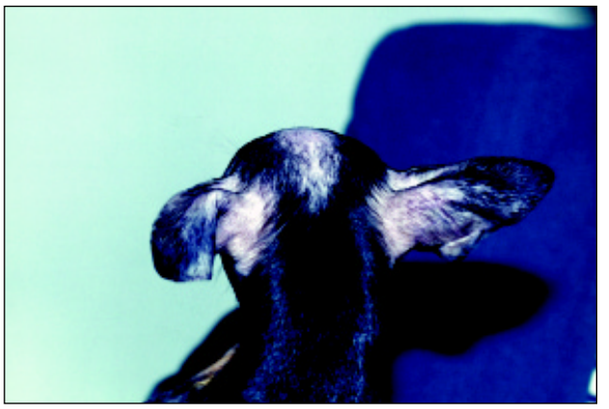

Figure 4—Bilateral alopecia on frontal region, ear base, and pinna. The condition of iatrogenic hyperadrenocorticism in this dog was caused by topical medication alone.

Figure 5—Hair color change from the original black color to white on the frontal and temporal regions in a dog with resolving iatrogenic hyperadrenocorticism. This is the same dog as in Figure 4.

Subnormal baseline cortisol levels and a suppressed or poor response in cortisol levels after ACTH administration were consistently found in all 28 dogs [Table 5]. The mean concentration of baseline cortisol before ACTH stimulation was 0.5 µg/dl and ranged from 0.1 to 1.6 µg/dl (reference range, 0.5 to 6 µg/dl). The mean concentration of cortisol one hour after ACTH administration was 1.1 µg/dl and ranged from 0.1 to 2.8 µg/dl (reference range, 8 to 18 µg/dl). Sixteen dogs (16/28) showed no response in cortisol levels after ACTH administration, whereas 12 dogs (12/28) had a suppressed response to ACTH.

After a diagnosis of IHAC was made, no medication was prescribed to these dogs except in those dogs (17/28) that suffered from secondary, generalized pyoderma. These dogs were prescribed cephalexin orally (25 to 35 mg/kg, *bid*) for four to eight weeks, depending on the severity of the skin conditions.

Twenty-eight dogs (28/28) recovered from their IHAC without progressing into secondary hypoadrenocorticism.

Table 3

Results of Laboratory Tests From 28 Dogs With Iatrogenic Hyperadrenocorticism

Value*	Reference Range	Mean	Standard Deviation	Range
RBC	4.2–7.9x10^6/µl	6.2	1.3	4.1–8.1
Hb	9.6–19.1 g/dl	14.7	2.9	9.5–19.3
Hct	28.4–53.1%	42.8	7.9	28.5–54.0
WBC	7,500–18,400/µl	15,567	7,163	7,100–46,000
neut	4,275–16,560/µl	12,298	1,401	4,606–44,160
eos	75–1,472/µl	249	265	0–882
lymph	375–5,888/µl	2,148	1,339	242–3,920
mono	75–1,288/µl	934	420	89–2,516
Alb	2.6–3.7 g/dl	3.4	0.4	2.5–4.5
ALKP	27–219 U/l	907	896	17–3,788
ALT	20–123 U/l	390	376	14–1,792
AST	6–60 U/l	91	70	6–431
BUN	7–27 mg/dl	18	8.6	4–70
Chol	115–243 mg/dl	289	125	120–500
Crea	0.5–1.3 mg/dl	0.9	0.4	0.4–3.6
Glu	82–127 mg/dl	156	63	97–313
TP	5.4–7.8 g/dl	6.7	0.6	5.3–7.7
Trig	30–87 mg/dl	119	75	26–388
Na	136–151 mmol/l	140	6	127–155
K	3.2–4.9 mmol/l	4.0	0.4	3.7–4.8
Cl	99–116 mmol/l	103	9	89–118
Na/K	27–42	35.7	3.9	29.4–51.3

* Hb=hemoglobin concentration; Hct=microhematocrit; RBC=red blood cell count; WBC=white blood cell count; neut=neutrophil; eosi=eosinophil; baso=basophil; lym=lymphocyte; mono=monocyte; Alb=albumin; ALKP=alkaline phosphatase; ALT=alanine transferase; AST=aspartate transferase; BUN=blood urea nitrogen; Cl=chloride; Chlo=cholesterol; Crea=creatinine; Glu=glucose; Na=sodium; K=potassium; TP=total protein; Trig=triglyceride

Mean time from initial withdrawal of medication to clinical improvement was six weeks. Cessation of polydipsia, polyuria, and polyphagia were the first signs of recovery, followed by weight loss and a tight-bellied appearance. At this stage, liver size had reduced, and hepatic enzyme levels were within the reference ranges for most dogs (24/28). Pyoderma and excessive hair loss or alopecia remained at this stage. It took a further mean time of 12 weeks (range, eight to 24 weeks) before there was a complete remission of these cutaneous lesions. However, color changes in patchy patterns of new hair growth were found in dogs (19/19) which previously had partial or generalized alopecia. The original white hair coat became darker, whereas the original dark or black hair coat became lighter or grayish [Figure 5]. Apart from color change in hair coat, calcinosis cutis (4/4) was the only cutaneous lesion that appeared to be permanent. Dogs with IHAC induced by topical medication exhibited complete remission of the hair coat changes at approximately five weeks after topical medications were withdrawn. Similar hair color changes were also observed in these dogs.

Three dogs (3/28) had concurrent diabetes mellitus while suffering from IHAC. Of these three dogs, the IHAC in two dogs was caused by systemic medication (parenteral triamcinolone once daily, intermittently for three years), with IHAC induced by topical 0.1% betamethasone ointment (twice daily over the entire body for three years to treat recurrent papules and pustules) in the third dog. All three dogs were ovariohysterectomized after the diagnosis of diabetes mellitus was made. Complete remission of IHAC also occurred in these three dogs. However, diabetes mellitus persisted and was controlled using isophane insulin[e] (0.25 to 1 U/kg subcutaneously, once daily).

Discussion

The cases of IHAC described in the present study showed many of the clinical signs consistent with hyperadrenocorticism described in other studies.[1–4] While many

Table 4

Abnormalities in Hematological and Biochemical Profiles* From 28 Dogs With Iatrogenic Hyperadrenocorticism

	No. of Dogs
Abnormal Findings on Hematological Profile	
Eosinopenia	18
Lymphopenia	7
Monocytosis	7
Abnormal Findings on Biochemical Profile	
Elevated ALP level	15
Elevated ALT level	14
Hypercholesterolemia	14
Elevated AST level	12
Hypertriglyceridemia	12
Hyperglycemia	10
Abnormal Adrenocortical Function	
No response in cortisol levels after ACTH stimulation	16
Suppressed cortisol level after ACTH stimulation	12

* ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; ACTH=adrenocorticotropic hormone

Table 5

Cortisol Levels Before and After Adrenocorticotropic Hormone (ACTH) Stimulation From 28 Dogs With Iatrogenic Hyperadrenocorticism

Case	PreACTH Cortisol (μg/dl)	PostACTH Cortisol (μg/dl)
1	0.1	0.2
2	0.5	0.4
3	0.3	0.3
4	0.2	0.3
5	0.5	0.2
6	0.1	2.8
7	0.1	0.1
8	0.3	0.4
9	0.1	2.6
10	0.1	0.3
11	1.4	2.4
12	1.6	2.6
13	0.1	0.1
14	1.6	2.3
15	0.1	0.1
16	0.1	0.1
17	0.1	0.1
18	0.5	1.0
19	0.4	2.6
20	0.9	2.2
21	0.8	2.0
22	1.6	2.6
23	0.3	0.6
24	0.1	0.1
25	1.1	2.2
26	1.1	1.0
27	0.1	0.3
28	0.8	2.0

breeds were included in this study, toy breeds were overrepresented. This was presumed to reflect the popularity of these breeds in this area[13] rather than a predisposition.

Although twice as many males as females were affected with IHAC, as yet no study has established that IHAC has a sex predisposition.

Clinical manifestations in these dogs were consistent with spontaneous hyperadrenocorticism.[1–4] Cutaneous abnormalities were the most common signs. Dogs with generalized thin hair coat or alopecia were found to have been medicated orally, parenterally, or both for preexisting skin disorders. In the cases of generalized thin hair coat, alopecia, or pyoderma, the lesions were initially noted on the face and head. Toward the end of the course, the back, flanks, hind legs, and tail became involved. Although the exact compounds of corticosteroids could not be confirmed in some cases using oral medication, the severity of excessive hair loss was related to routes of administration. Regardless of duration, topical medications (skin, ear, or eye preparations) induced mild and localized rather than generalized hair loss or alopecia.

Apart from skin manifestations, polydipsia, polyuria, lethargy, and polyphagia were also consistent with spontaneous hyperadrenocorticism.[1–4] The severity of these signs was also found to be related to the routes of medication. Observable signs were only evident in dogs which were medicated orally, parenterally, or both for preexisting skin disorders. None of these signs developed in dogs that were given only topical treatment.

Eosinopenia and lymphopenia, which have been frequently reported in dogs with spontaneous hyperadrenocorticism,[1–4] were the most common findings in the hematological profiles in these dogs. However, only dogs which were medicated via oral or parenteral administration showed these findings. In the present study, elevated levels of ALP, ALT, and AST were the most common abnormalities in the biochemical profiles, and these findings agreed with most published studies.[1–4] All dogs

demonstrating a pot-belly and hepatomegaly also had elevated levels of hepatic enzymes. In those dogs with hypercholesterolemia and hypertriglyceridemia, raised levels of hepatic enzymes were also found.

Diabetes mellitus is one of the medical complications associated with hyperadrenocorticism. Glucocorticoids increase gluconeogenesis, act as an insulin antagonist, and can induce a diabetic state.[14] In the present study, the concurrent diabetes mellitus in three dogs was not thought to be caused by glucocorticoid abuse alone because these dogs were obese, aged, and intact females.[15] Progesterone, one of the insulin antagonists, rises dramatically during diestrus. Therefore, older bitches may occasionally develop diabetes during diestrus.[15] Together with the action of another insulin antagonist, exogenous glucocorticoids, diabetes mellitus then developed. In the authors' three cases, ovariohysterectomy was performed and the glucocorticoids medication discontinued, and the signs of IHAC showed complete remission. However, the condition of diabetes mellitus persisted but was well controlled with insulin.

The HPA axis in dogs is easily suppressed by exogenous glucocorticoids. These glucocorticoids suppress the HPA axis in 12 to 36 hours after administration and suppress the levels of cortisol via the negative feedback mechanism.[5,7,11,12] The ACTH stimulation test has been proven to be a sensitive indicator of adrenocortical suppression and an excellent means of determining a return of the HPA axis to normal function.[1,2,4,5] However, dogs with hypoadrenocorticism also have a suppressed HPA axis.[1,3,4] The cause of hypoadrenocorticism can be either spontaneous or iatrogenic. Secondary iatrogenic hypoadrenocorticism was considered as the major differential diagnosis in the present study. Adrenal gland atrophy due to a severely depressed HPA axis can be caused by long-term corticosteroid abuse.[3,11,12,16] Secondary iatrogenic hypoadrenocorticism can be induced by long-term corticosteroid use with sudden withdrawal.[16,17] The pathophysiological changes characteristic of hypoadrenocorticism are serum electrolyte alternations. Lack of aldosterone secretion, as a result of adrenocortical insufficiency, leads to impaired serum sodium and chloride conservation and potassium excretion. Significant hyponatremia and hyperkalemia develop, and the sodium to potassium ratio decreases.[16,17] The ACTH stimulation test and the blood sodium to potassium ratio can be used as aids in the differential diagnosis between IHAC and secondary iatrogenic hypoadrenocorticism.[1,16,17] In the present study, the blood sodium to potassium ratio was monitored every two to four weeks for each dog until complete remission. The blood sodium to potassium ratios of the 28 dogs in this study were within reference range during the course of IHAC. All dogs recovered from IHAC without developing secondary iatrogenic hypoadrenocorticism.

It is known that topical application of corticosteroids rapidly suppresses the HPA axis, with plasma cortisol concentrations becoming significantly depressed within seven hours after the first treatment.[8,9] Repeated topical applications of corticosteroids will continue to suppress plasma concentrations of ACTH and cortisol and continue to reduce the response to exogenous ACTH.[7,11,12] Prolonged treatment for three weeks or more induced marked suppression of the adrenal gland's response to exogenous ACTH in dogs.[10–12] The duration and dosage of systemic corticosteroid administration to induce clinical signs of IHAC in dogs have not been determined but appear to be dependent on the type of corticosteroids used and their duration of action (i.e., higher doses of longer-acting preparations appeared to induce IHAC more rapidly than the other glucocorticoid preparations used). Although the exact compounds of corticosteroids used could not be confirmed in all 28 dogs of this study, the compounds for both parenteral and topical preparation may be short-acting (as with hydrocortisone), intermediate-acting (as with triamcinolone), or long-acting (as with betamethasone and dexamethasone).[2,4] These compounds are widely available in parenteral, skin, ophthalmic, and aural preparations.

In the present study, the mean time for initial clinical signs of IHAC to develop was around nine months, although signs did develop in as little as one month. It has been shown that after cessation of corticosteroid therapy, HPA axis returns to normal values by four weeks after the last daily treatment in dogs treated with triamcinolone acetonide or with betamethasone valerate.[12] In the present study, the HPA axis of these dogs was not monitored after medication was withdrawn due to lack of cooperation from the owners.

It took an average of six weeks for dogs to show clinical improvement or a return to normal hepatic enzyme levels after corticosteroid withdrawal. On average, it took another 12 weeks for skin and hair coat conditions to exhibit complete recovery, except for calcinosis cutis and the hair color changes which persisted. For those cases that were induced by topical application of corticosteroids, complete recovery of their hair coat and skin conditions occurred within five weeks after the topical application was discontinued.

Conclusion

Iatrogenic hyperadrenocorticism is a common endocrinopathy seen in the authors' hospital. Twenty-eight dogs with a history of long-term oral, parenteral, or topical glucocorticoid use were examined. The most common clinical findings were consistent with spontaneous hyperadrenocorticism, including cutaneous lesions and elevated levels of ALP, ALT, and AST. The ACTH stimulation test was the best test to differentiate spontaneous hyperadrenocorticism from IHAC. The blood so-

dium to potassium ratio was a helpful indicator to differentiate IHAC from secondary iatrogenic hypoadrenocorticism. The pathophysiological change characteristic of hypoadrenocorticism is a decreased serum sodium to potassium ratio. Among these cases, clinical signs and abnormalities in laboratory tests were less remarkable in dogs with IHAC induced by topical corticosteroids in comparison to those with the same condition caused by parenteral or oral corticosteroids. Also, a shorter period of time was required to exhibit complete remission of this condition in dogs when it was induced by topical corticosteroids rather than by parenteral or oral corticosteroids.

[a] Sysmex K-1000; Toa Medical Electronics Co., Ltd., Japan
[b] Kodak Etachem DT 60 II; Eastman Kodak Company, Rochester, NY
[c] Cortrosyn; Organon, Oss, Holland
[d] Coat-A Count Cortisol; Diagnostic Products Cooperation, Webster, TX
[e] Insulatard HM; Novo Nordisk A/S, Denmark

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