Mitotane (o,p′-DDD) treatment in a cat with hyperadrenocorticism

An 11-year-old male castrated Persian cat with spontaneous hyperadrenocorticism was presented. Both adrenals were grossly enlarged and calcified. A diagnosis of pituitary-dependent hyperadrenocorticism was made. Signs of hyperadrenocorticism resolved with long-term mitotane treatment. Concurrent diabetes mellitus resolved after 220 days of therapy. No severe adverse drug reactions were noted.

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INTRODUCTION

Hyperadrenocorticism is a rare endocrine disorder in cats. Approximately 60 cases of spontaneous feline hyperadrenocorticism have been described or mentioned in the veterinary literature (Swift and Brown 1976, Meijer and others 1978, Peterson and Steele 1986, Helton-Rhodes and others 1993, Myers and Bruyette 1994a, Peterson and others 1994, Duesberg and Peterson 1997). The treatment regimens described include unilateral or bilateral adrenalectomy, medical therapy with mitotane (o,p′-DDD), ketoconazole and metapyrone, and ^{60}Co irradiation. Currently, the recommended treatment is unilateral or bilateral adrenalectomy (Zerbe 1989, Peterson and others 1994). Although mitotane treatment in cats has been described, there are no detailed reports of long-term treatment.

CASE HISTORY

An 11-year-old male castrated Persian cat with newly diagnosed diabetes mellitus was referred after a hypoglycaemic crisis to establish glycaemic control and to evaluate possible hyperadrenocorticism. The cat had received a first dose of regular insulin (H Insulin; Hoechst), of unknown quantity, the same morning.

On initial presentation, the cat was depressed, slightly dehydrated and the mucous membranes were pale. Body temperature was 37·9°C. A potbellied appearance, hair loss on the ventral abdomen, very thin skin with prominent veins and some degree of muscle atrophy were noted (Fig 1). Palpation of the abdomen revealed an enlarged liver.

Emergency blood analysis showed an elevation of urea (25·0 mmol/litre) with normal creatinine. Blood glucose was 4·1 mmol/litre. An intravenous infusion of lactated Ringer's solution was commenced and blood glucose levels monitored. Insulin was withheld until further tests could be performed.

Laboratory evaluation several hours after initial treatment revealed moderate leucocytosis with an increase in mature neutrophils and lymphopenia (Table 1). The packed cell volume was normal, but anisocytosis, polychromasia and nucleated red blood cells were noted. The blood chemistry profile showed a markedly elevated blood glucose level and mild azotaemia. Liver enzymes were raised except for alkaline phosphatase and gamma glutamyl transferase. Lipids were increased. Total protein was markedly elevated but electrophoresis showed a normal distribution pattern. Electrolyte values were within the reference ranges. Negative test results were obtained for feline leukaemia and feline immunodeficiency viruses and the feline infectious peritonitis titre was 1:400.

Radiography (Fig 2) showed a distended abdomen with good contrast due to fat accumulation. The liver was enlarged and there were some gas-filled bowel loops. Both kidneys were well delineated and normal in size. Cranial to the kidneys an oval opacification with calcification was noted. The calcification was visible on both sides of the spinal column on the ventrodorsal view.

Ultrasonographically, both adrenal glands could be readily visualised. The left adrenal measured 34 × 25 × 30 mm, the right adrenal 38 × 39 × 27 mm (Fig 3). They were heterogeneous in structure with focal acoustic shadowing. The enlarged liver was hyperechoic but homogeneous, as were the renal cortices. No other abnormalities were found.

A low-dose dexamethasone screening

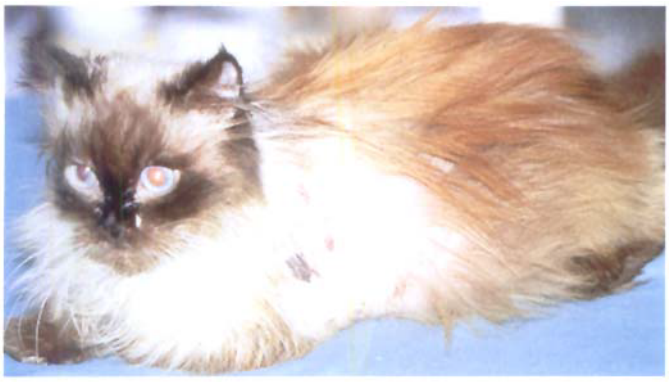

FIG 1. The cat at initial presentation, showing marked alopecia and several bruises

Table 1. Complete blood count and blood chemistry analysis shortly after admission

Parameter	Result	Reference range
Complete blood count		
Packed cell volume (%)	37	27–47
White blood cells (/μl)	15·40	5·50–19·50
Mature neutrophils (/μl)	13·86	2·50–12·50
	(90%)	(50–77%)
Lymphocytes (/μl)	770	1·5–7·0
	(5%)	(17–41%)
Monocytes (/μl)	616	0–850
	(4%)	(<4%)
Eosinophils (/μl)	154	0–1·5
	(1%)	(<6%)
Chemistry profile		
Glucose (mmol/litre)	27·5	3·0–6·7
Urea (mmol/litre)	13·5	3·3–10·8
Creatinine (μmol/litre)	88·5	<168
Total triglycerides (mmol/litre)	2·20	0·57–1·14
Cholesterol (mmol/litre)	6·1	1·8–3·9
Alanine aminotransferase (U/litre)	90	<70
Aspartate aminotransferase (U/litre)	34	<30
Lactic acid dehydrogenase (U/litre)	630	<200
Gamma glutamyl transferase (U/litre)	0	<4
Alkaline phosphatase (U/litre)	53	<140
Total bilirubin (μmol/litre)	10·3	<8·5
Total protein (g/litre)	102	57–78

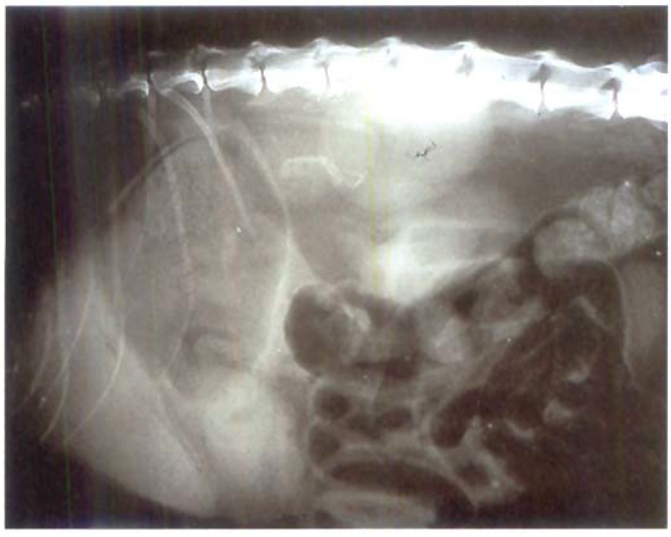

FIG 2. Lateral abdominal radiograph. The adrenals are enlarged and calcified

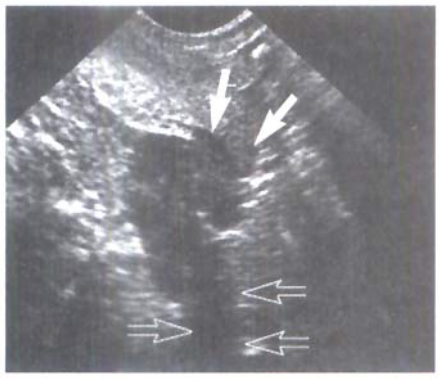

FIG 3. Ultrasonogram of the right adrenal gland which is grossly enlarged and hypoechoic. The caudal vena cava lies immediately adjacent to the adrenal (closed arrows). Distal to the caudal third of the gland an acoustic shadow can be seen (open arrows). The marks on the scales indicate a distance of 10 mm

Table 2. Results of serial ACTH testing on plasma cortisol determinations*

Day	Baseline value (nmol/litre)†	Stimulation value (nmol/litre)‡
18	232	309
47	52	218
69	39	235
111	30	5·5
146	19	17
280	11	33

* at 0 and 30 minutes after administration of 0·125 mg tetacosactrin intramuscularly
† Reference range 8·150
‡ Reference range 165·330

test was performed by administering 0·01 mg/kg dexamethasone intravenously and collecting blood samples at zero, four and eight hours. The baseline value of cortisol was 7 nmol/litre (reference range 8 to 150). A suppression was noted after four hours, but not after eight hours (11 and 69 nmol/litre, respectively). An adrenocorticotropic hormone (ACTH) stimulation test was not performed at this stage.

Based on the clinical, radiographic, ultrasonographic and laboratory results a tentative diagnosis of pituitary-dependent hyperadrenocorticism (PDH) was made.

Insulin therapy was commenced and maintained at 3 units of lente insulin (Insulin Lente; Novo Nordisk) twice daily.

At this stage the cat developed a skin lesion with concurrent fever that was treated with enrofloxacin (Baytril; Bayer). Two weeks later the skin lesion had healed, the cat was well but insulin dosage had to be increased to 4 units twice daily. Bilateral adrenalectomy was advised but the owner strongly favoured nonsurgical treatment. The cat was treated with 25 mg/kg mitotane (Lysodren; Bristol-Myers) daily. Therapy with fludrocortisone (Astonin H; Merck) at 0·01 mg/kg and prednisolone at 0·3 mg/kg, administered orally in the evenings, was commenced on day 3. This treatment was well tolerated except for a transient decrease in appetite on days 4 and 5.

An ACTH test (Table 2) was performed on day 18 of mitotane therapy by injecting 125 μg of tetracosactrin (Synacthen; Ciba) intramuscularly and measuring the increase in plasma cortisol after 30 minutes (Johnston and Mather 1979, Kemppainen and others 1984). Prednisolone and mineralocorticoids had been omitted the previous evening. Cortisol levels were high and mitotane dosage was increased to 37·5 mg/kg/day. As no further decrease in

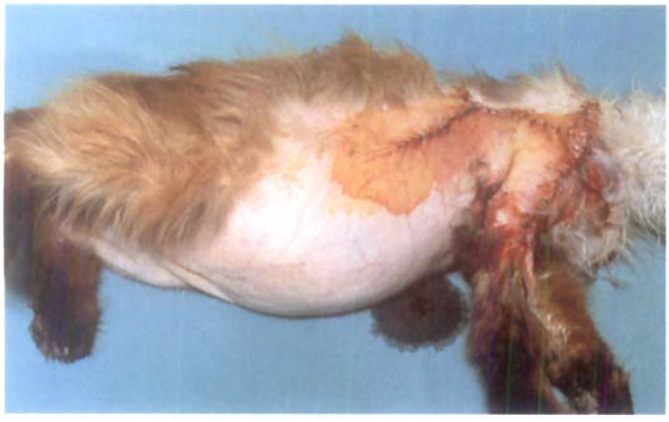

FIG 4. The cat immediately after surgery. Note the extremely thin, folded skin, the prominent veins and the pendulous abdomen

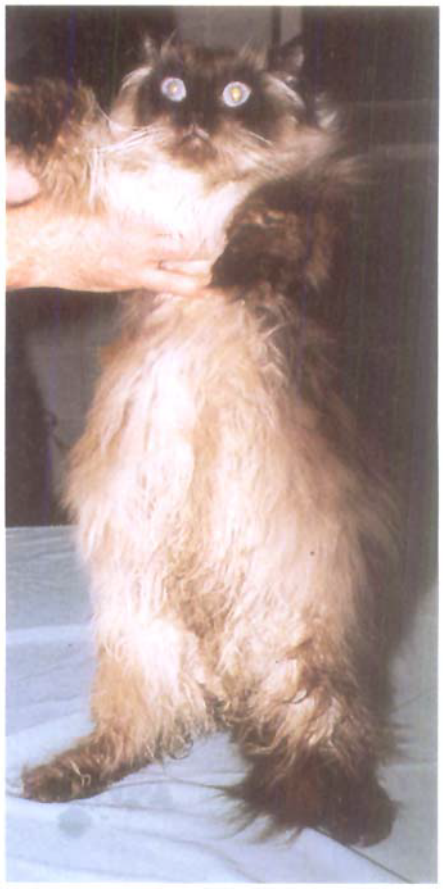

FIG 5. The cat two years after commencement of mitotane therapy

adrenocortical function could be achieved between days 47 and 69 it was decided to try a maintenance protocol with 50 mg/kg/week without corticoid or mineralocorticoid supplementation.

Two weeks later the cat presented with extensive patches of thin torn necrotic skin that required extensive surgery (Fig 4). Wound healing was slow but uncomplicated. Sutures were removed 18 days after surgery.

Hair started to regrow and glycaemic control was maintained but the cat required increasing amounts of insulin (2 × 7 units). Three weeks after institution of maintenance therapy the cat suffered an acute hypoglycaemic crisis and insulin was decreased to 2 units twice daily.

The results of an ACTH test performed on day 111 led to the reinstitution of mineralocorticoid and corticoid therapy. Mitotane was discontinued on day 146. Insulin dosage was further reduced and eventually stopped on day 220 after the initiation of mitotane treatment.

The cat was in good condition and clinical signs of hyperadrenocorticism had resolved. The abdomen had decreased in size and tension and the adrenal glands could now be palpated. This had not been possible on initial examination. A follow-up radiograph demonstrated no changes in adrenal size and calcification.

On day 280 recurrence of polydipsia and thinning of the haircoat was noted. The blood glucose level was slightly above normal. ACTH testing showed considerable stimulation (Table 2) and mitotane was administered again at 25 mg/kg/day for one week and then 37·5 mg/kg/day.

Due to inappetence, dosage was reduced to 12·5 mg/kg/week after three months.

At the time of writing, the cat had been on this treatment for 12 months, showing no signs of hyperadrenocorticism or any adverse reactions (Fig 5). Serial blood examinations during the whole treatment did not show abnormalities.

DISCUSSION

Although hyperadrenocorticism is an uncommon disease in cats there has been an increasing number of reports during the past few years (Swift and Brown 1976, Meijer and others 1978, Peterson and Steele 1986, Helton-Rhodes and others 1993, Myers and Bruyette 1994a, Peterson and others 1994, Feldman 1995, Duesberg and Peterson 1997).

Clinical features resemble those observed with canine hyperadrenocorticism in many respects. Affected cats mostly show increased appetite, polydipsia, polyuria, poor hair condition and a pendulous abdomen.

There are, however, some apparent differences. The vast majority of cats suffer from overt diabetes mellitus, a feature that is noted in only approximately 10 per cent of canine patients with hyperadrenocorticism (Zerbe 1989, Myers and Bruyette 1994a, Peterson and others 1994, Feldman 1995). However, diabetic cats seem to do much better after successful therapy of hyperadrenocorticism than dogs: most cats could be stabilised on a much lower insulin dosage or insulin therapy could be stopped altogether (Feldman and others 1989, Zerbe 1989, Myers and Bruyette 1994a). The cat presented in this report had overt diabetes mellitus that resolved after successful treatment.

Another typical condition in feline hyperadrenocorticism is an extremely fragile skin that tends to tear spontaneously, creating large wounds that are prone to infection in these already immunosuppressed patients (Scott and others 1982, Daley and others 1993, Helton-Rhodes and others 1993). This cat, too, suffered from skin lesions several times during the course of treatment necessitating antibiotic therapy for prolonged periods of time and quite extensive surgery at one point. Additionally, antibiotic treatment was given twice when harsh lung sounds were discovered on auscultation. Fortunately the cat did not develop life-threatening infections.

Another feature observed on the radiographs were the grossly enlarged and calcified adrenals (Fig 2). Calcification of the adrenals in cats is not unusual (Peterson and others 1994), but there are only two reports of histological evidence of calcified adrenal glands in cats with hyperadrenocorticism (Swift and Brown 1976, Immink and others 1992).

Calcifications here were prominent enough to be detected radiographically. Ultrasonographically, acoustic shadowing was evident. Neither adrenal decreased in size during treatment, as determined by follow-up radiography.

Polydipsia and polyuria in hyperadrenocorticoid cats has been attributed to

an early development of diabetes mellitus and subsequent osmotic diuresis (Peterson and others 1994, Feldman 1995). However, there are reports of cats with hyperadrenocorticism which show polydipsia and polyuria without having diabetes mellitus (Feldman and Nelson 1987, Immink and others 1992). This cat, too, showed increased thirst along with hair coat deterioration when the relapse occurred. Blood glucose level was 8·6 mmol/litre at that time. This was the same level as had been measured one month before when water intake and the serum fructosamine value (Reusch and Hoyer-Ott 1995) had been normal (216 µmol/litre, reference range <340). As 8·6 mmol/litre is well below the threshold for glucosuria in cats, osmotic diuresis seems very unlikely to be the sole reason for the increased thirst. However, glucosuria cannot be entirely excluded from a spot sample.

The blood profile performed within hours of admission (Table 1) revealed changes rather typical of hyperadrenocorticism and diabetes mellitus. Noteworthy is the marked elevation in total protein. As the cat was clinically dehydrated some degree of hyperproteinaemia is expected. Glucocorticoid administration can lead to hyperproteinaemia in human beings (Werner and others 1989) and in normal dogs (Moore and others 1992) and might be possible in cats as well. A coronavirus infection was, however, initially considered. When total protein was checked on frequent later occasions it turned out consistently to be 'high normal'.

The presence of nucleated red blood cells in conjunction with a normal red blood cell count leads to the diagnosis of a subclinical regenerative anaemia of unknown origin masked by dehydration. Stimulation of the bone marrow is known to occur in bitches with hyperadrenocorticism but this usually leads to erythrocytosis (Feldman 1995).

Testing protocols for hyperadrenocorticism in cats are not as established as they are in dogs. Dexamethasone suppression tests have been performed with dosages from 0·01 to 1·0 mg/kg intravenously (IV) and orally (Johnston and Mather 1979, Medleau and others 1987, Smith and Feldman 1987). Whereas dosages of 0·01 and 0·1 mg/kg (IV) do not lead to complete adrenocortical suppression for eight hours in all healthy cats, dosages of 1·0 mg/kg (IV) reliably suppress cortisol levels for up to 32 hours (Smith and Feldman 1987, Bruyette 1994). Differentiation between PDH and functional adrenocortical tumour in clinical cases might be possible using very high-dose dexamethasone suppression tests (Bruyette 1994).

In this case, the results of the dexamethasone suppression test and the symmetrical appearance of both adrenals led to a diagnosis of PDH.

ACTH levels, unfortunately, could not be determined due to the lack of validated assays for feline ACTH. A computed tomography scan was not performed.

ACTH stimulation testing is not a conclusive test for hyperadrenocorticism in cats. It is reliable, though, for the diagnosis of hypoadrenocorticism (Bruyette 1994, Myers and Bruyette 1994b). Intramuscular injection of 0·125 mg tetracosactrin, an ACTH analogue in aqueous solution and determination of cortisol levels at baseline and 30 minutes were chosen from various reported protocols (Johnston and Mather 1979, Kemppainen and others 1984, Smith and Feldman 1987, Bruyette 1994). Cortisol determinations were performed using high-pressure liquid chromatography. As endogenous cortisol and prednisolone cannot be differentiated by this method it was necessary to omit the steroid administration on the preceding evening.

It is striking that on day 18 of treatment the basal cortisol concentration was high (232 nmol/litre) with only a moderate increase (to 309 nmol/litre) after ACTH administration, which is considerably less than would be expected in a dog with a comparable baseline value. Healthy cats tend to have lower post-ACTH cortisol values than do dogs (Duesberg and Peterson 1997). Another explanation would be slow or incomplete resorption of ACTH from the injection site leading to the cortisol peak being missed by the blood sampling. Inadvertent drug administration by the owner would lead to similar results.

In cats, bilateral adrenalectomy has been recommended as the treatment of choice for PDH (Zerbe 1989, Peterson and others 1994). When mitotane treatment was first introduced, information about this treatment regimen was sparse. Mitotane had been used in four healthy cats (Zerbe and others 1987, Zerbe 1989) and in one cat with hyperadrenocorticism (Feldman and Nelson 1987, Nelson and others 1988) with an inconsistent efficacy in suppressing adrenocortical function. It had been well tolerated, however. Since then, two reports have been published suggesting that mitotane might be effective in treating cats with PDH when given on a long-term basis (Myers and Bruyette 1994a, Feldman 1995). In the present case, mitotane was given at moderate levels (25 mg/kg/day) for 10 weeks, then for 11 weeks at 50 mg/kg/week. After a pause of 19 weeks, daily mitotane therapy was resumed for 13 weeks and then decreased to 12·5 mg/kg/week as continuous therapy.

The treatment regimen followed in this case was derived from the protocol for dogs described by Rijnberk and Belshaw (1995), aiming at the complete destruction of all three zones of the adrenal cortex leading to both glucocorticoid and mineralocorticoid deficiency. In contrast, mineralocorticoid deficiency develops with conventional mitotane therapy in only about 5 per cent of dogs (Feldman 1995, Peterson and Kintzer 1997). As mineralocorticoid deficiency is a potentially life-threatening disease with the possibility of acute crises, fludrocortisone (a mineralocorticoid) was administered in conjunction with maintenance doses of prednisolone during the induction phase. No abnormalities in either the clinical appearance of the cat that were suggestive of hypoadrenocorticism or in the sodium or potassium concentrations were detected during this period. When adrenocortical

function seemed stable after day 69, corticoid and mineralocorticoid supplementation was stopped and only reinstituted after an ACTH stimulation test gave evidence of hypoadrenocorticism on day 111.

Mitotane was well tolerated with only slight adverse reactions. Interestingly, progress in destroying adrenocortical function was very slow initially. The same observation has been made by Nelson and others (1988) and Feldman (1995). After approximately three months of mitotane therapy, a decrease in adrenocortical function was suddenly very obvious leading to a hypoglycaemic crisis that was attributed to the decrease in insulin antagonists. An ACTH stimulation test was consistent with hypoadrenocorticism. Induction of hypoadrenocorticism had been intended but unfortunately a relapse occurred and the cat had to be placed on a maintenance protocol on low dosage that at the time of writing had been working well for 12 months.

It is well known that cats do not respond as readily to mitotane therapy as dogs (Zerbe 1989, Myers and Bruyette 1994a, Feldman 1995). There are no published experimental studies, so it can only be hypothesised which factors might be responsible.

After intestinal resorption, mitotane requires conversion into an intermediate metabolite (o,p'-DDA) to be active. The drug's two effects are mitochondrial destruction leading to cell death and direct inhibition of steroid synthesis (Peterson and Kintzer 1997). Species differences in resorption and activation of the drug and variations in tissue susceptibility could be an explanation for the reduced effectiveness in cats. An increased metabolism of the drug, which is disposed of by hepatic microsomal enzymes, seems highly unlikely in the cat.

In this case, the daily dose of mitotane was 25 mg/kg at the beginning and 37·5 mg/kg after day 18, which is lower than the induction dosages recommended for dogs (Rijnberk and Belshaw 1995). This, of course, could have contributed to the delayed therapeutic response.

Why the cat responded abruptly after changing to 50 mg/kg once weekly remains unclear. Two possible explanations include a cumulative effect of mitotane and a relatively high susceptibility of the adrenal cortex to a high dose pulsed therapy.

Conclusions

This case suggests that mitotane treatment in cats with PDH might be possible. In cats, much longer periods of drug administration seem to be necessary than for dogs. Whereas cats with bilateral adrenalectomy need to be monitored very closely in the perioperative and early postoperative periods, mitotane treatment requires frequent control examinations for the rest of the animal's life because of sudden changes in corticoid production and insulin requirement. This involves much dedication on the part of the owner. However, more investigation is needed in this field before general recommendations for treatment can be made.

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