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The use of trilostane in a cat with pituitary-dependent hyperadrenocorticism

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The Queen Mother Hospital for Animals, Royal Veterinary College, Hawkshead Lane, North Mymms, Hatfield, Herts. AL9 7TA UK.
• Feline hyperadrenocorticism is much less frequently reported in cats than in dogs and consequently treatment protocols are less well established.

• Mitotane, ketoconazole and metyrapone have all been used in cats with variable success, but the treatment of choice remains bilateral adrenalectomy.

• Trilostane, an inhibitor of steroid synthesis that has been used to control hyperadrenocorticism in dogs, may provide an alternative for medical management of feline hyperadrenocorticism, particularly in cases where severe debilitation makes surgery more hazardous.

A seven and a half year old, neutered male domestic short-haired cat was referred to the Queen Mother Hospital for Animals, Royal Veterinary College because of a history of chronic suppurative skin infections and recurrent abscessation, particularly over the hocks. Dermatological problems had begun approximately 3-4 months prior to referral. The owners reported polyuria and polydipsia and a voracious appetite over the past month. The cat had gained some weight (weight at time of referral 7.2kg [15.8lb]) and had developed a pendulous abdomen. The remainder of the coat had become unkempt. A large, ulcerated area, which was resistant to healing, had developed between the scapulae. Treatment prior to referral had included multiple courses of antibiotics but the response to treatment had been poor. Blood work had been performed two months ago at which time the cat had shown a mild hyperglycaemia (221mg/dl, reference range 68-126mg/dl) and had a mild elevation in alanine aminotransferase (199U/l, reference range 58-150U/l) and a marked increase in serum globulin (68g/l, reference range 26-51g/l).

At the time of referral the cat was dull and depressed. His coat was poor and seborrhoeic and there was alopecia of the nose, ventral abdomen and hindlimbs. He had a plantigrade stance and large, (sagging? soft?) abscesses covered the accessory tarsal bones bilaterally, extending proximally and distally down the hind limbs. There was bilateral popliteal lymphadenopathy. The cat was reluctant to move and had a low, crouching gait with instability of the right hock that led to a gait abnormality. He had generalised muscle wasting and thin skin with multiple skin tears around his neck and shoulders,
some of which had merged to form large ulcerated areas. There was palpable hepatomegaly but no other abdominal abnormalities.

We performed a complete blood count and biochemistry panel, along with thoracic and abdominal radiographs and abdominal ultrasound. An ACTH-stimulation test\(^a\) was carried out and urine was collected for analysis. Considerable skin bruising developed around the jugular venopuncture site. Swabs for bacterial culture were taken from the hock abscesses. Blood results showed a neutrophilia (14.09 x10\(^9\)/l, reference range 2.5-12.5 x10\(^9\)/l) and lymphopenia (0.16 x10\(^9\)/l, reference range 1.5-7.0 x10\(^9\)/l), minor increases in amylase (1475U/l, reference range 750-1200U/l), lipase (354U/l, reference range 0-90U/l) and alkaline phosphatase (170U/l, reference range 35-140U/l), and hyperglycaemia (437mg/dl, range 68-126mg/dl). Alanine aminotransferase was within reference ranges. The urine had a specific gravity of 1.032, 3+ glucose, 2+ protein, 2+ blood and abundant yeast cells were found in the urine sediment. Culture of the urine yielded a pure growth of \textit{Candida albicans}. Radiography revealed hepatomegaly. Abdominal ultrasonography identified both adrenal glands greater than 7mm in dorsoventral width. The liver had a diffusely increased echogenicity. ACTH-stimulation test\(^a\) results revealed a basal cortisol of 197nmol/l rising to 307nmol/l 60 minutes and 354nmol/l 120 minutes after administration of ACTH\(^a\). Bacterial culture of the pus from the hock abscesses yielded a mixed growth of bacteria including \textit{Escherichia coli} and \textit{Klebsiella} species that were sensitive to enrofloxacin and ampicillin respectively.

Although the clinical signs and history were suggestive of pituitary-dependent hyperadrenocorticism with secondary diabetes mellitus, the ACTH-stimulation test that we performed was not conclusively diagnostic. The cat’s owners declined further invasive testing, however, nor were they able to cover the cost of a magnetic resonance scan to identify a possible pituitary tumour. The cat remained hospitalised for 7 days and the hock abscesses were drained, bathed and flushed with sterile saline twice daily. Treatment was started with protamine zinc insulin\(^b\) (2IU, s/q, q 24 hrs) as well as ampicillin\(^c\) (20mg/kg [9.1mg/lb] PO q 8 hrs) and enrofloxacin\(^d\) (2.5mg/kg [0.1mg/lb] PO, q 12 hrs for two weeks) to resolve the skin infections. We also began treatment with the
steroid synthesis inhibitor trilostane® (30mg, PO, q 24 hrs.) with a view to monitoring the cat’s response to this drug and reaching a presumptive diagnosis through a positive response to treatment. No specific treatment for the funguria was given as it was hoped that this would be cleared once the diabetes and hyperadrenocorticism were under control. An ACTH-stimulation test® was repeated before the cat was discharged from the hospital. A summary of the ACTH-stimulation test® results from this (day 7) and subsequent examinations is shown in Table 1.

Two weeks later the owners reported an improvement in the cat’s general demeanour and activity levels. His appetite for water and food had decreased, though he was still eating well. The hock lesions had partially resolved and though the skin tears between the scapulae were still ulcerated, they were cleaner and showed signs of re-epithelialisation. A biochemistry profile, urine analysis, total T4 measurement and ACTH-stimulation test® were repeated (Table 1, day 21). Biochemical parameters were all within normal limits. The T4 was slightly low at 18.6nmol/l (range 19-65nmol/l). Urine analysis, including sediment examination, was unremarkable. A 24-hour glucose curve showed that although the initial response to insulin was good and the glucose nadir 7-8mmol/l (3.8-7.0mmol/l), the insulin was not lasting 24 hours and the glucose had risen to 21.8mmol/l (3.8-7.0) by the following morning. On the basis of these results the daily insulin dose was split into two doses of 1IU, to be given twelve hours apart.

Although the cat improved clinically on trilostane®, and the diabetes was well controlled, the skin lesions around the cat’s neck persisted and we decided to increase the trilostane dose to 30mg twice daily to try to achieve better disease control. One month later the cat showed signs of further improvement and the ACTH-stimulation test® revealed an increased degree of steroid synthesis inhibition (Table 1, day 50). The skin lesions on the neck and shoulders were almost completely resolved. Bilateral adrenalectomy was discussed with the owners as a way of controlling the hyperadrenocorticism in the long-term but they were reluctant to have surgery performed and were concerned about the problems related to impaired wound-healing following laparotomy. Follow-up examinations were taken over by the referring practice from this time.
Six months after the start of treatment the cat developed an increased appetite for water and increased frequency of urination. He was therefore referred back to the Queen Mother Hospital for investigation. His appearance had not altered and his skin was still in good condition. Abdominal palpation could identify only one kidney and abdominal radiographs showed that the left kidney was much smaller than the right. Urine analysis revealed that yeast infection was present (urine culture yielded a growth of *Candida albicans* in excess of $10^6$ organisms/ml) and blood work revealed a mild elevation in serum globulin (52.9g/l, range 26-51g/l) as well as hyperglycaemia (28.3mmol/l, range 3.8-7mmol/l). The cat began treatment using the anti-fungal agent itraconazole\(^f\) (10mg/kg [4.5mg/lb] PO q 12 hrs.). Several repeated urine analyses performed at the referring veterinary practice showed no change in the degree of *Candida* infection in the urinary tract. After three weeks the drug was changed to fluconazole\(^g\) (50mg/kg [22.7mg/lb] PO q 12 hrs). The fungal infection of the urinary tract proved refractory to treatment and renal function began to deteriorate. Ten months after the start of therapy for hyperadrenocorticism the cat became anorexic and began to vomit. He was found to be severely azotaemic (urea 80.5mmol/l, reference range 1.5-12mmol/l, creatinine 1177µmol/l, reference range 90-200µmol/l) and did not respond to, or improve, following conventional fluid therapy. The owners elected to euthanase the cat at this point and a post mortem examination was carried out.

Post mortem examination identified disparity between the sizes of the kidneys with the left kidney appearing shrunken and irregular in outline (Fig – picture of kidneys) while the right kidney was enlarged. The left kidney had marked destruction of the renal medulla, replaced by white purulent exudate, with cortical atrophy. The cut surface of the right kidney appeared normal. The adrenal glands were enlarged (1cm in diameter). A large pituitary mass was visible extending rostrally, running over the optic chiasm and protruding 3-4mm rostral to the optic chiasm (Fig – picture of brain). Serial slicing of the fixed brain revealed the pituitary mass extending dorsally into the brain, forming a well-demarcated, roughly spherical mass 12-15mm in diameter.
Histological examination of the left kidney showed prominent moderate multifocal cortical fibrosis and lymphoplasmacytic inflammation. The Bowman’s capsule was thickened and there was mineralisation of the Bowman’s capsule and renal tubules. Moderate lymphoplasmacytic inflammation and mineralisation of renal tubular basement membranes was present also in the renal medulla. The renal pelvic cavity contained abundant fungal organisms (Candida species) which extended along the ureter. The right kidney was similarly affected but to a much lesser degree. Both adrenal glands had symmetrically enlarged cortices, reaching up to 5mm in depth.

The pituitary mass was composed of polyhedral cells with a large pale stippled nucleus and moderate amounts of pale eosinophilic cytoplasm. There was mild anisokaryosis and occasional mitoses. The cells were divided by thin connective tissue septa and blood vessels, with a tendency to pallisade around blood vessels. Mild focal haemorrhage was present. The surrounding intensely eosinophilic cells were compressed by the mass. These features were considered typical of a chromophobe pituitary adenoma that had expanded dorsally into the overlying brain. The diagnosis of pituitary-based hyperadrenocorticism was thus confirmed retrospectively.

Feline hyperadrenocorticism is much more rare than the disease in dogs and differs also in the common presenting signs. As in dogs, most cases (81%) are pituitary-based and are caused by excessive ACTH release by neoplastic or hyperplastic ACTH-secreting cells\(^1\). Cats frequently present with extreme skin fragility and skin infections. Severe skin problems are considered an indicator of poor prognosis. Polyuria and polydipsia, so often the main presenting sign in dogs, typically develop later in the disease and are due to the development of diabetes mellitus and an osmotic diuresis rather than to direct cortisol effects\(^2\). Duesberg and Peterson\(^1\) report an incidence of diabetes mellitus of 83% in cats with hyperadrenocorticism. Since the time of their extensive review, several case studies and series have been published, including information detailing a further 19 cats\(_2\) of which 13 were diabetic (68%)\(^3,4,5,6,7\). Although this figure is lower, it shows that diabetes mellitus is still much more common in cats with hyperadrenocorticism than in dogs where the incidence is around 5-10%\(^8\).
This case illustrates the problems in reaching a diagnosis of hyperadrenocorticism in cats using a conventional screening test. ACTH-stimulation tests have been reported to be difficult to interpret in cats with systemic diseases, particularly diabetes mellitus or hyperthyroidism, because basal cortisol levels are typically higher and the response to stimulation tends to be more dramatic. This can lead to an over-diagnosis of hyperadrenocorticism in the cat. In this case, the converse was true and the cat in this study failed to respond to ACTH up to the levels expected for a cat with hyperadrenocorticism (post-ACTH cortisol > 450nmol/l or >16µg/dL). Previously described cases of hyperadrenocorticism have shown that only 51% of cats have an exaggerated response to ACTH, while 16% were borderline and the remainder were within the normal range quoted. In two reported cases clinically suggestive of hyperadrenocorticism but where hypercortisolemia could not be documented, other steroid hormones, particularly progesterone, were measured and found to be elevated. Both of the cats in these reports had adrenal masses, however, and it is unlikely that the cat described here had a similar secretory profile. The dexamethasone suppression test has also been used as a screening test in cats, although there is some contention about the dose required to achieve adrenal suppression. The recommended dose of dexamethasone varies between 0.01-0.1mg/kg with 15-20% of normal cats failing to suppress at a dexamethasone dose of 0.01mg/kg. Again, the specificity of this test is questionable in cases where there is concurrent disease. Some authors suggest that a magnetic resonance scan to identify a possible pituitary tumour is a useful diagnostic test to run on cats with diabetes mellitus who present with insulin resistance and report finding a pituitary mass in all four cats suspected of being hypercortisolemic. The cat in this report did not present for insulin resistance and had not been recognised as having diabetes mellitus until referral to the Queen Mother Hospital but a magnetic resonance scan would have been a useful diagnostic test in this case and would have reinforced our tentative ante-mortem diagnosis.
Although mitotane (o,p’-DDD) has been the drug of choice for the treatment of canine hyperadrenocorticism for the past 10-15 years\textsuperscript{13}, in cats this drug has been found to give variable results\textsuperscript{14,15,16,17}.

Two enzyme inhibitors have been used to control hyperadrenocorticism in cats. One, ketoconazole, the primary use of which is for the treatment of mycotic disease, has been used with success in humans and dogs, but again has found to have unpredictable results in cats\textsuperscript{18}. Willard et al., \textsuperscript{18} were, however, measuring the plasma cortisol response to ketoconazole in healthy animals. When a second group of cats with hyperadrenocorticism were treated, only two of five showed clinical improvement\textsuperscript{19}. Ketoconazole has the added disadvantage of being associated with a risk of side effects including nausea, vomiting, anorexia\textsuperscript{18}, elevated liver enzymes, jaundice\textsuperscript{20} and thrombocytopenia\textsuperscript{19}. Metyrapone is the second enzyme inhibitor to be used to treat cats with hyperadrenocorticism\textsuperscript{21,22}. It is an inhibitor of 11-\(\beta\)-hydroxylase in the steroid synthesis pathway and thus interferes with cortisol and corticosterone (and consequently aldosterone) synthesis. In one report of its use, metyrapone was documented to cause transient hypocortisolaemia followed by escape from the effects of enzyme inhibition, presumably mediated by an increase in plasma ACTH levels, although endogenous ACTH was not measured in this cat\textsuperscript{21}. Its use is recommended as a pre-treatment prior to bilateral adrenalectomy, particularly in cases where there are large skin deficits and the prospects for effective wound healing are poor. There is a problem with the availability of metyrapone, however, and for this case, we were unable to find a supplier.

Trilostane is an inhibitor of 3\(\beta\)-17 hydroxysteroid dehydrogenase that blocks the synthesis of adrenal and gonadal steroid hormones. It has been used for the treatment of hyperadrenocorticism in dogs with good results\textsuperscript{23,24}, but its use has not been reported in cats. The subject of this report began medication with trilostane at a dose of 30mg once daily, though at 7.2kg a higher dose (60mg) would probably have been used in a canine patient. Monitoring the response to treatment was complicated by the fact that the ACTH-stimulation test was within the normal range in the initial patient evaluation. Clinically, however, the cat improved and his skin lesions began to resolve. A second
improvement was noticed following the increase in dose to 30mg twice daily and at this point the refractory skin lesions over the cat’s neck and shoulders were closed for the first time. Work in dogs has shown that trilostane has a relatively short duration of action (Neiger\textsuperscript{25} ref) and it is possible that the same is true in cats and that more regular dosing is required for optimal control of clinical signs. Trilostane caused no adverse effects in the subject of this study and the drug appeared to be tolerated well at both the original and higher doses.

Funguria is infrequently reported in the cat, but is more common in cats where there is concurrent, immunosuppressive disease or other predisposing factors (e.g. indwelling urinary catheters)\textsuperscript{26, 27}. The prognosis for spontaneous control of urinary fungal growth is good, so long as the primary disease is addressed and controlled\textsuperscript{27}. In this case it appears that the urinary tract infection was never truly cleared and eventually led to renal insufficiency. Earlier and more aggressive anti-fungal therapy may have improved the outcome though the prognosis for cats with renal fungal infection is poor\textsuperscript{27}. That this secondary, opportunistic infection was so difficult to manage suggests that the cat’s hyperadrenocorticism was not adequately controlled by trilostane or that the diabetic control was inadequate. Serial glucose curves showed that the cat’s glucose stayed below 15mmol/l for 75% of the day and only became refractory to insulin treatment when there was a proven active urinary tract infection so it seems more likely that immunosuppression was secondary to hyperadrenocorticism\textsuperscript{28}. Thus, although trilostane improved the condition of the cat, most notably the refractory skin infections and abscesses, it was not effective in reversing all of the metabolic consequences of hyperadrenocorticism at the dose used.

Most authors agree that bilateral adrenalectomy is the treatment of choice for cats with hyperadrenocorticism as medical therapy has been found to be unrewarding\textsuperscript{3, 14, 29}. Surgery is, however, associated with a high incidence of intra-operative and post-operative complications\textsuperscript{29} though these are less frequently reported in cats than for dogs\textsuperscript{30}. A significant number of problems center on the skin fragility and the incidence of wound breakdown and contamination\textsuperscript{14}. Though trilostane was not entirely successful in
this case, it was able to improve the cat’s condition and allow the cutaneous wounds to heal. Trilostane may therefore be a useful adjunct to surgery for long-term management of feline hyperadrenocorticism and would provide an alternative to metyrapone.
a  Synacthen (tetracosactrin acetate), Alliance Pharmaceuticals Ltd, Chippenham, Wiltshire, UK

b  Insuvet protamine zinc insulin, Schering-Plough Animal Health, Welwyn Garden City, UK

c  Amfipen (ampicillin), Intervet, Cambridge, UK

d  Baytril (enrofloxacin), Bayer plc, Bury St Edmunds, Suffolk, UK

e  Modrenal (trilostane), Wanskerne Ltd., St Austell, Cornwall, UK

f  Sporonox (itraconazole), Janssen Pharmaceuticals Ltd, Co Cork, Eire

g  Difulcan (fluconazole), Pfizer Ltd., Sandwich, UK
References:

2. Scott DW, Manning TO and Reimers TW. Iatrogenic Cushing’s syndrome in the cat. *Feline Pract* 1982;12:30-36


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<th>Time from start of trilostane treatment (days)</th>
<th>Cortisol pre-ACTH (nmol/l)</th>
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* Follows trilostane dose increase.

Table 1: Results from sequential ACTH-stimulation tests pre and post-treatment with trilostane.