Persistent isolated hypocortisolism following brief treatment with trilostane

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Key words (not included in title) Addison's, Cushing's, disease, adrenal, necrosis, atypical, ultrasound

Summary

A 12-year-old male neutered Miniature Poodle with confirmed pituitary dependent hyperadrenocorticism was treated with trilostane. After three doses it developed clinical and laboratory changes suggestive of isolated hypocortisolism ('atypical hypoadrenocorticism') which persisted and progressed for more than 3 months despite immediate withdrawal of the trilostane. The clinical signs of hyperadrenocorticism resolved without further trilostane. After 3 months prednisolone treatment was started and the clinical signs of hypocortisolism resolved. Prednisolone therapy was required for more than 1 year. Ultrasonography initially demonstrated large hypoechoic adrenal cortices, typical of dogs with hyperadrenocorticism which then became small and heteroechoic, consistent with the development of adrenal necrosis. Persistent isolated hypocortisolism has not been reported previously as a complication of trilostane therapy. The case is also remarkable for the very short duration of trilostane therapy that elicited this complication. Clinicians should be aware that trilostane therapy may result in adrenal necrosis even in the very earliest stages of therapy but prompt action can prevent a life-threatening situation.

Abbreviations used

ACTH	Adrenocorticotropin
HAC	Hyperadrenocorticism (HAC)
IV	Intravenously
LDDST	Low dose dexamethasone suppression test
MUVH	Murdoch University Veterinary Hospital
PD-HAC	Pituitary dependent hyperadrenocorticism

SC	Subcutaneously
UK	United Kingdom

Trilostane is a synthetic, hormonally-inactive, steroid that competitively inhibits steroid synthesis by blocking the action of 3β hydroxysteroid dehydrogenase. Trilostane has been found to be an effective treatment for dogs with pituitary dependent hyperadrenocorticism in several published trials totalling more than 120 dogs.[1, 2, 3] Current evidence suggests that its principle effects in the dog are on cortisol secretion: aldosterone production is relatively unaffected.[4] The median survival time of dogs treated with trilostane is not significantly less than that achieved with mitotane.[5] Minor side effects are sometimes seen with trilostane, such as mild lethargy, decreased appetite and slight electrolyte abnormalities.[1] However the incidence of side effects in these studies (15%) was lower than that reported with mitotane (25%).[6] Hypoadrenocorticism is only rarely seen during trilostane treatment (3 % of treated cases) but is more common during mitotane treatment (5 to 17% of treated cases) .[6, 7]

Trilostane's mechanism of action suggests that it would not be expected to cause permanently low cortisol levels (hypocortisolism). Any endocrinological abnormalities induced by trilostane should dissipate rapidly following withdrawal of the drug. In the largest published study to date of 78 dogs receiving trilostane, hypoadrenocorticism was confirmed in two dogs, one of which resolved after trilostane was withdrawn[1]. A further two dogs died of unexplained causes shortly after starting therapy.

Recently a case was reported in the UK of a dog that developed severe adrenal necrosis and hypoadrenocorticism following a 21 day course of trilostane[8]. In this short communication we describe an Australian dog with PD-HAC that developed isolated hypocortisolism and ultrasonographic evidence of adrenal necorosis after only three doses of trilostane. This is the first report of permanent isolated hypocortisolism associated with adrenal changes in a dog treated with such a brief course of trilostane.

Isolated hypocortisolism is sometimes referred to as ‘atypical hypoadrenocorticism’. Veterinary practitioners should be aware of this potential, though rare, side effect of trilostane therapy.

Case report

A 12-year-old neutered male Miniature Poodle was initially presented to the emergency service of Murdoch University Veterinary Hospital (MUVH) with a history of frequent vomiting over the previous 8 hours and a longer history of recurrent intermittent vomiting and diarrhoea over the past few years with the last episode being a month previously. The vomitus consisted mostly of food; bile and blood were not present. On clinical examination, the dog was noted as being obese and had partial truncal alopecia. Further questioning of the owner revealed a 1 year history of polyuria, polydipsia and marked polyphagia. There had also been an episode of dermatitis in the previous year. Routine blood samples at the referring practice had been obtained 1 week before this episode and analysed using an in-house analyser. There was a marked increase in alkaline phosphatase (AP) (1393 IU/L [reference range is 23 to 212 IU/L]) and alanine transaminase (ALT) (200 IU/L [reference range is 10-100 IU/L]). These changes were felt to be consistent with hyperadrenocorticism although an association with of the previous illness could not be discounted. Blood samples were taken on admission to MUVH for electrolytes, a packed cell volume and total solids (assessed by refractometery). The results were within reference limits. An ultrasound examination of the abdomen was performed. The liver was subjectively enlarged with a mild, diffuse increase in echogenicity suggested by the fact that portal markings were just visible. The left and right adrenal glands were plump in appearance though both retained their normal shape (see Figure 1). Both adrenal cortices were hypoechoic. No other abnormalities were detected, and importantly the pancreas appeared to be normal. These changes were considered to be consistent with pituitary dependant

hyperadrenocorticism.[9] No cause of vomiting or diarrhoea was evident and no specific diagnosis was made. The dog recovered well with symptomatic therapy (intravenous fluids, ranitidine 2mg/kg IV twice daily and one injection of methadone 0.3mg/kg SC). The vomiting resolved 9 hours after admission and the dog was discharged back to the referring practice with advice that the long history of polyuria/poydipsia and polyphagia should be further investigated.

The dog was then diagnosed 1 week later with hyperadrenocorticism (HAC) using both the adrenocorticotropin (ACTH) stimulation test and the low dose dexamethasone suppression test (LDDST). Cortisol concentrations were measured in a local commercial veterinary laboratory (VetPath, Ascot, WA) using a solid phase competitive chemiluminescent enzyme immunoassay (DPC Immulite Cortisol assay, Diagnostic Products Corporation, Los Angeles, California) the results of which have been shown to be well correlated with the results of radio-immunoassays previously validated in the dog.[10] The ACTH stimulation test showed evidence of moderate overstimulation with cortisol concentrations increasing from 96 nmol/L to 806 nmol/L. Greater than 600 nmol/L is considered to be consistent with the diagnosis of HAC.[11] During the LDDST the cortisol concentrations were initially 117 nmol/Lwith moderate suppression of 40 nmol/L at 4 hours post-dexamethasone and escape of suppression by 8 hours-post dexamethasone with levels rising to 64.9 nmol/L. Greater than 40 nmol/L is considered to be consistent with the diagnosis of HAC.[11] The results also strongly suggested that the condition was pituitary dependent.[11] As the acute vomiting episode was less than 24 hours in duration and 1 week had elapsed between the previous episode of illness and these endocrine tests, the effect of the illness was not likely to have had significant impact on the results. The existance of clinical signs and routine blood tests that were consistent with HAC before the development of the acute vomiting episode lend further evidence that the results of the endocrine tests could be taken as confirmation of HAC.

The dog was started on treatment for hyperadrenocorticism with trilostane 6 weeks later, obtained from a compounding pharmacist in Australia, at a dose rate of 5 mg/kg. However, after only three doses (60mg each) had been given to the dog, it was presented to the MUVH emergency centre with another episode of vomiting and diarrhoea; this time it was systemically unwell. On clinical examination there were no changes from previous examinations except the dog was dehydrated. The PCV was 0.55 L/L and total solids measured by refractometery were 90g/L. The sodium concentration was 137 mmol/L and the potassium was 4.7 mmol/L when measured on a hand-held emergency analyser (i-STAT, Heska Corporation, Fribourg, Switzerland). The dog was given small quantities of an oral rehydration solution (Lectade: Jurox Pty Ltd) and two doses of metoclopramide (0.3mg/kg SC). The dog's condition improved quickly and it was discharged the following day without further investigations.

Trilostane treatment was stopped by MUVH emergency centre and the dog's condition improved temporarily. However, when the dog was presented 3 months later to the medicine service at MUVH, the owner reported intermittent bouts of vomiting and diarrhoea, as well as the complaint that the dog was licking its legs a lot more and was refusing normal food on a regular basis. There was no evidence of polyuria or polydipsia. There had also been a weight loss. The dog had weighed 12 kg but now weighed 10.5 kg. Body condition score at this time was 6 out of 9.

On clinical examination, it was noted that the coat was regrowing and there was saliva staining on both forelimbs and paws, suggesting pruritis. These findings, in combination with the lack of appetite, led to a suspicion that the dog no longer had HAC and was in fact suffering from hypoadrenocorticism. A serum biochemistry panel was measured using a fully automated clinical chemistry analyser (Rx Daytona; Randox (Australia) Ltd., Parramatta, NSW) which demonstrated that the AP concentration had declined to 77 iu/l. This would not be expected in a dog with HAC

that had not been treated in 3 months. No electrolyte abnormalities were identified (sodium was 139 mmol/L (reference range = to) , potassium was 5.1 mmol/L (reference range = to) (the Rx daytona uses ion selective electrodes). An ACTH stimulation test demonstrated that the pre and post ACTH cortisol concentrations (measured by the same method and in the same commerical laboratory as described above) were 25.8 and 26.5 nmol/L respectively. Abdominal ultrasonography demonstrated that the liver remained subjectively moderately enlarged with rounded borders and a mildly echogenic uniform texture. The portal vasculature was more visible than on the previous examination and the liver was less echogenic than the spleen. This suggested that the changes in liver echogenicity associated with hyperadrenocorticism were less marked. Both of the adrenal glands had reduced in size. The left adrenal gland had lost it's normal 'kidney' shape and was irregular in appearance with a mottled, mixed echogenicity. It was surrounded by a small rim of bright echogenic fat. The right adrenal gland was more difficult to image however it was more uniform in texture and echogenicity. The surrounding fat was normal in appearance. The appearance of the adrenal glands was felt to be consistent with adrenal necrosis with some evidence of periglandular inflammation on the left. The concentration of aldosterone was measured in the pre ACTH sample (which was also the sample used for the serum biochemistry reported above) by a local human hospital using a commercial human radio-immunoassay (DPC Coat-A-Count Aldosterone assay; Diagnostic Products Corporation, Los Angeles, California) and was found to be less than 70 pmol/L. No reference range for canine serum has been validated by this laboratory however the published ranges for pre-ACTH aldosterone concentrations in canine samples measured using similar human assays is 0 to 300 pmol/L.[12] In the absence of electrolyte abnormalities it was felt that there was no evidence of mineralocorticoid defiency and therefore no specific mineralocorticoid treatment was prescribed.

The dog was treated with prednisolone (0.5 mg/kg orally once daily) for 2 weeks and responded very well. Within 24 hours its appetite had returned to normal, it had shown enthusiasm for exercise and was generally more active. The dog remained well for 3 months after which the dose of prednisolone was gradually tapered. Within 7 days of stopping prednisolone the dog developed signs of hypocortisolism again and an ACTH stimulation test was repeated. The pre and post ACTH cortisol concentrations were 22.7 and 22.4 nmol/l respectively. Prednisolone was restarted and the dog recovered and remains well (although is still receiving prednisolone) a further 12 months later. Several attempts were made to reduce the prednisolone dose during this time but each time the dog became unwell (lethargic). Electrolytes were rechecked once in this time and were found to be within the reference ranges.

Subsequent analysis using high pressure liquid chromatography of the trilostane capsules obtained from the compounding pharmacist confirmed that they contained the correct dose with minimal quantities of ketotrilostane.

Discussion

The diagnosis of PD-HAC was confirmed in this dog using the widely accepted criteria of appropriate clinical signs and response to specific endocrinological tests.[11] The subsequent regrowth of hair, reduction in polyphagia and loss of body weight would be consistent with successful trilostane treatment. Occasionally steroid–responsive clinical signs, such as pruritus, may be unmasked in dogs treated successfully for HAC. The recurrence of a pruritic condition in a dog following trilostane treatment has been observed by others.[11] However, the clinical signs of lethargy and vomiting that this dog developed are not consistent with successful trilostane therapy and would be consistent with overt glucocorticoid deficiency.[13, 14] Moreover, as sodium and potassium concentrations remained normal, suggesting an adequate aldosterone concentration,

this dog appears to have developed isolated hypocortisolism, also known as atypical hypoadrenocorticism. The fact that the clinical signs did not resolve in the 3 months following withdrawal of the drug, but did respond to prednisolone therapy, suggests that this isolated hypocortisolism was a persistent state rather than temporary state. The withdrawal of the therapy 3 months later and the immediate recurrence of the signs is also evidence of the persistence of this hypocortisolaemic state.

The cause of this isolated hypocortisolism is most likely to be selective or partial adrenal necrosis although no adrenal biopsies were obtained in this case. The changes in the ultrasonographic appearance of the adrenal glands are highly suggestive that this is the explanation. The ultrasonographic appearance of the adrenal glands in this case are in marked contrast to those described for dogs that are treated for extended periods with trilostane.[15] It could be argued that the clinical signs may have been caused by another disease rather than overt hypocortisolism. However no evidence of another disease was found on routine blood screens or abdominal ultrasound (specifically including the pancreas).

This case has some similarities to one recently reported in the UK[8]. The dog in this earlier report developed bilateral adrenal necrosis and associated clinical signs of hypoadrenocorticism after 21 days treatment with trilostane. Electrolyte abnormalities were identified although aldosterone concentrations were not measured. In contrast, the case reported here developed isolated hypocortisolism after only three doses of trilostane. The consistent lack of electrolyte abnormalities makes a mineralocorticoid deficiency highly unlikely but to formally demonstrate this aldosterone should have been measured on one or more of the samples obtained after ACTH stimulation as most reference ranges for aldosterone include very low concentrations. Unfortunately these samples were not retained for this analysis. The short duration of therapy and the different nature of the endocrine abnormality from the case of Chapman and others

(2004) makes this case report both new and of interest to any veterinarian who prescribes trilostane. The use of trilostane is increasing within Australia (Dechra Pharmaceuticals, data on file) and therefore similar cases may occur in the future.

Although adrenal necrosis has only been previously reported as a complication of trilostane administration in one case, a syndrome of prolonged suppression of adrenocortical function in dogs receiving trilostane has been reported in abstract form.[8, 16] All of the dogs in this abstract did continue to require trilostane albeit at a lower dose. Although adrenal gland histopathology was not described in these cases, the syndrome may also represent a milder form of adrenal necrosis.

The development of persistent isolated hypocortisolism and ultrasonographic changes in adrenal architecture cannot be explained by current knowledge of trilostane's actions. It is known that the duration of action of trilostane is short.[17] Although serum cortisol concentrations may be undetectable for a few hours after dosing, they quickly return to normal levels. This short term suppression of adrenocortical function generally provides good long-term control of hyperadrenocorticism in most patients.[1] In some cases the drug is so short acting that the frequency of dosing has to be increased from once to twice daily.[17] Recent work suggests that the effects of trilostane on steroidogenesis may not be limited to inhibition of the enzyme 3β hydroxysteroid dehydrogenase.[18] However no data presented by Sieber-Ruckstuhl and her colleagues would explain the changes observed in this case or that of Chapman and his colleagues.

The link between hypocortisolaemia and trilostane administration in this case is purely temporal. It is possible that this may have been a coincidence and other causes of adrenal necrosis are possible. Trilostane might cause adrenal necrosis by accumulating to toxic levels within the adrenocortical cells. Alternatively trilostane may

induce programmed cell death (apoptosis) as an idiosyncratic reaction in certain dogs without reaching cellular concentrations that would be considered toxic. The drug might also induce vascular changes or act in a haptogenic capacity to stimulate an adverse immune response. The pathological findings of Chapman and others are not consistent with these latter two theories. More dogs need to be studied and clinicians should be encouraged to submit adrenal glands from dogs that have died following any drug administration.

It should be noted that ACTH administration has been associated with an increased risk of bilateral adrenal haemorrhagic necrosis in man and it alone may cause degeneration and focal necrosis of the adrenal cortex.[19] Dogs frequently receive synthetic ACTH in the days before trilostane is dispensed and it is possible that this may be a contributing factor in some cases of adrenal necrosis. In this particular case the time delay from the diagnosis to the administration of trilostane was nearly 5 weeks and so synthetic ACTH is not likely to have been a factor. However it has been shown that dogs receiving trilostane show an increase in serum concentrations of endogenous ACTH.[20] It is possible that the three doses of trilostane caused an immediate increase in endogenous ACTH and this lead to adrenal necrosis.

Spontaneous remission of HAC has been reported previously and was presumed to result from embolisation of a pituitary microadenoma with subsequent normalisation of adrenal function.[11] Few details are presented on the five dogs with this syndrome and it is not known if they developed temporary or permanent hypocortisolism, or if the suspected pituitary lesions were confirmed using advanced diagnostic imaging modalities or pathology, or if the adrenal glands were similarly examined.

Clinicians should be aware that the response of dogs to trilostane is very variable. Many dogs require a change in dose (increase or decrease) and much higher doses

than the initial starting doses may be required in some cases.[3] The efficacy of the drug has to be monitored in each patient and adjustments made as necessary. Veterinarians using trilostane should be aware that it may rarely cause adrenal gland necrosis and potentially acute iatrogenic hypoadrenocorticism or isolated hypocortisolism. Awareness of this complication will help to ensure a good prognosis. Despite this case report, trilostane should still be considered an effective and safe drug to use in the treatment of HAC.

Acknowledgments

We thank Kenwick Veterinary Hospital for referring the dog and student Adelie Wong and the staff of the Murdoch Pet Emergency Centre for their help with the management of the case. We would also like to thank Dechra Pharmaceuticals for perfoming the analysis of the trilostane capsules. Ian Ramsey was a visiting academic clinician at Murdoch University during the time that this case was presented.

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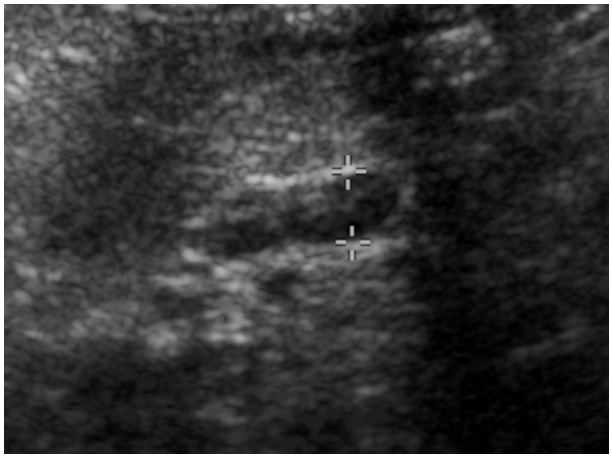
Figures (to also be supplied separately)

Figure 1

Adrenal ultrasonograph from a 12 year old neutered male Miniature Poodle performed at the time of diagnosis of hyperadrenocorticism. The cranial pole of the left adrenal (a) measured 7.8 mm, however the caudal pole was slightly smaller at 6.6 mm. The right adrenal (b) had a similar, plump appearance, and a slightly larger cranial pole (8.6 mm) compared to the caudal pole (6.4 mm).

a)



b)

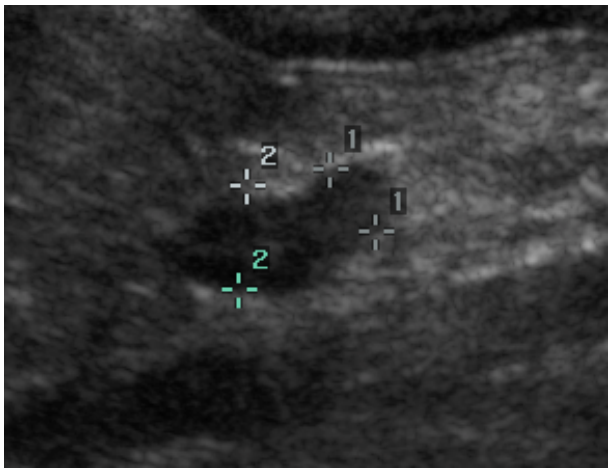
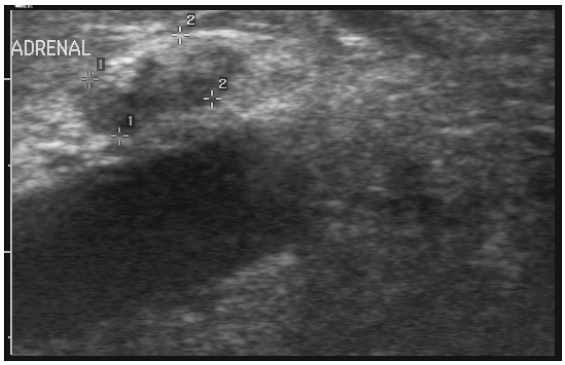


Figure 2

Adrenal ultrasonograph from a 12 year old neutered male Miniature Poodle performed at the time of diagnosis of isolated hypocortisolism. The cranial pole of the left adrenal (a) measured 3.8 mm and the caudal pole measured 4.2 mm The cranial pole of the right adrenal gland (b) measured 4.6 mm and the caudal pole 5.2 mm right adrenal

a)



b)