Trilostane in Dogs

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Synopsis

Over the last 10 years trilostane, a competitive inhibitor of steroid synthesis, has become widely used for the treatment of canine hyperadrenocorticism. Trilostane causes a significant but reversible decrease in cortisol production and a concomitant improvement in clinical signs in most dogs with this common condition. Side effects, though infrequent, can be serious: dogs treated with this drug require regular monitoring. This review summarises current knowledge of the use of this drug with particular emphasis on its efficacy, safety, adverse reactions and effects on endocrine parameters. Brief mention is made of its other uses in dogs and other species.

Introduction

Trilostane (4,5-epoxy-17-hydroxy-3-oxoandrostan-2-carbonitrile) is a synthetic steroid whose ability to reduce adrenocorticotrophic hormone (ACTH) stimulation of adrenal corticoids was first described 40 years ago [1]. Further studies demonstrated that it was orally active and that its mode of action was as a competitive inhibitor of steroid synthesis [2]. The use of trilostane was investigated in various human conditions, including hyperadrenocorticism (HAC), hyperaldosteronism and breast cancer [3-7]. Although it did appear to have some effect on some cases of human HAC it was not as effective as other available treatments and in a recent consensus statement is no longer considered as a treatment option [8]. It is, however, still used in the treatment of human breast cancer [9].

The first report of the use of trilostane in canine HAC was by Hurley and others (1998) who successfully treated a series of 15 dogs, including 2 with adrenal dependent disease [10]. In the following decade many other abstracts and papers have followed. Trilostane was first authorised in the UK in 2005 for the treatment of canine HAC but has since been authorised in many other countries, most recently in the US. Human and imported veterinary

formulations are often used in those countries were it is not currently authorised for veterinary use.

The information contained within this paper is intended for an international audience and some information (e.g. doses) may be at variance with national recommendations. Veterinarians should consult their national regulatory authorities or local commercial representatives if they are unsure as to their local rules and guidelines.

Mode of Action

Trilostane is a competitive inhibitor of the 3β-hydroxysteroid dehydrogenase/isomerase system (3β-HSD), an essential enzyme system for the synthesis of several steroids including cortisol and aldosterone [2]. This enzyme catalyses the conversion of the 3β-hydroxysteroids (pregnenolone, 17-hydroxypregnenolone and dehydroepiandrosterone (DHEA)) to the 3-ketosteroids (progesterone, 17-hydroxyprogesterone and androstenedione) (see diagram 1). Trilostane does not appear to have any direct hormonal activity of its own and does not interact with the main sex hormone receptors [11].

Most studies on trilostane's mode of action have been performed in vitro, in laboratory rats or in humans. There is little information on the effect of trilostane in healthy dogs. In dogs with HAC it has been shown that trilostane causes a significant increase in 17 hydroxypregnenolone and DHEA concentrations [12]. These results confirmed an inhibitory effect of trilostane on the 3β-HSD. However, these authors also noted that 17-hydroxyprogesterone concentrations did not change in dogs treated with trilostane despite a marked decrease in cortisol concentrations. They postulated that, in addition to its inhibitory effect on the 3β-HSD system, trilostane has an influence on the 11β-hydroxylase and possibly on the interconversion of cortisol and cortisone by 11β-hydrozysteroid dehydrogenase (11β-HSD) [12]. However further studies by the same group demonstrated that cortisone concentrations in normal dogs are increased by ACTH [13]. This does not consistently happen in human beings, which suggests that the 11β-HSD enzyme in dogs is subtly different from the human equivalent. In addition cortisone concentrations in dogs with pituitary dependent HAC (PDH) are consistently increased; again this is in contrast to the situation in human beings [13]. Trilostane treatment reduces cortisone (both basal and following stimulation with ACTH) in dogs with PDH but to a lesser extent than it reduces cortisol concentrations [13].

Therefore, although trilostane may have an effect on 11β-HSD, until more is known about the canine version of this enzyme it is not possible to say this with any certainty.

Pharmacology

Few pharmacokinetic studies have been performed on trilostane. In the rat and monkey trilostane is rapidly absorbed after oral dosing with peak blood concentrations occurring between 0.5-1 hour (rat) and between 2-4 hours (monkey) [14]. In human volunteers the peak concentrations were between 2 and 4 hours [15]. In dogs peak trilostane concentrations are seen within 1.5 hours and decrease to baseline values in about 18 hours (Dechra Veterinary Products Limited, UK, data on file). The variability exhibited in systemic levels of trilostane following oral administration is possibly due in part to suboptimal absorption owing to its low water solubility. It has been shown that feeding immediately after the administration of trilostane increases its absorption [16]. Trilostane is cleared from the blood after 7 hours in the rat, 6-8 hours in the human and 48 hours in the monkey. Following the administration of trilostane to rats, the metabolite ketotrilostane is formed within a few minutes [17]. Ketotrilostane has about 1.7 times the activity of trilostane in steroid inhibition [15]. Conversely, when ketotrilostane is given to rats, trilostane is rapidly formed, suggesting that these compounds exist in equilibrium *in vivo*. Trilostane and ketotrilostane are metabolised into any one of 4 further metabolites. Excretion in rats is mainly via faeces, whilst in monkeys urinary excretion is more important [14].

Use in canine pituitary dependent hyperadrenocorticism

The clinical use of trilostane in canine HAC, and in particular PDH, has now been evaluated in several published clinical studies from centres across the world [18-23]. In addition unpublished studies have been conducted for regulatory purposes (Dechra Veterinary Products; data on file). Many other studies of the specific endocrine effects of trilostane have also been published but insufficient clinical data is presented to assess this aspect. Direct metanalysis of the combined data from these studies is not useful as the study populations (referral or first opinion; PDH only or all HAC), diagnostic evaluations, starting doses, monitoring methods, dose adjustment protocols and end points vary between the studies. However comparison of these published studies is worthwhile and is summarised in Table 1. It should be noted that some of these studies were funded, at least in part, by commercial sources.

Starting dose and frequency

The starting dose of the 6 studies listed in Table 1 ranged from 0.5 mg/kg twice daily to 20mg/kg once daily. To some extent the available formulations determined this choice. The finishing dose range in each study was even more variable however the mean/median dose was in the range 2.8 to 7.3 mg/kg in 5 of the studies (although in two of these studies the dose was split twice daily). It therefore seems logical therefore to recommend a starting dose the range 2 to 5 mg/kg per day.

There are no studies which directly compare different frequencies of trilostane administration. Four of the studies in Table 1 used once daily dosing as the starting point [18-20, 23]. However it has been demonstrated that the effect of trilostane on basal and ACTH stimulated cortisol is considerably less than 24 hours in most cases [24]. In the same study the authors also documented six dogs with HAC whose clinical signs were poorly controlled and whose post-ACTH concentrations observed four and 24 hours after the administration of trilostane were always higher than the equivalent cortisol concentrations in four dogs whose clinical signs were controlled. When four of the poor controlled dogs were switched to twice daily dosing, the clinical condition of three of them improved and their cortisol responsiveness to ACTH stimulation was reduced after both four and 24 hours. Following the publication of these results two studies opted to start dogs on a twice daily regimen [21, 22]. However the overall results obtained in these two studies were not superior to those obtained by earlier studies [18-20]. It is likely that at least a few dogs require twice daily dosing with trilostane to achieve control; however, it is probably not necessary to divide the starting dose for all dogs. In one study in which trilostane was used twice daily in all dogs there was a higher rate of adverse incidents than in any of the other five studies in Table 1 [21].

Monitoring

In the 6 studies listed in Table 1 the frequency of monitoring is one of the most consistent features. However the basis for this frequency is not clear. The caution of the early studies may not be appropriate now that more is known about the response to trilostane. In particular the clinical signs and cortisol concentrations continue to improve in most dogs in the first month [18, 20]. Performing an ACTH stimulation test 10 to 14 days after starting therapy is likely not to be so useful as changing the dose at this stage would risk increasing the dose of trilostane too early. Very few cases indeed develop trilostane overdosage in the first 2 weeks

of therapy. A review consultation should be adequate and an ACTH stimulation test only performed if adverse effects have been noted. Monthly monitoring for the first 3 months followed by 3 monthly monitoring for the first year followed by 4 to 6 monthly monitoring thereafter may well be adequate.

Most clinical studies to date have used the clinical signs and the ACTH stimulation test as the primary methods of assessing control [18-23]. In these studies trilostane caused significant reductions in both the mean basal and post-ACTH stimulation cortisol concentrations in dogs with HAC in the first month of treatment. Furthermore these improvements were also maintained in the study populations for the duration of the trial. However, despite its widespread use, the ACTH stimulation test has never been validated for trilostane therapy.

The ACTH stimulation test does provide a valuable assessment of the immediate capacity of the adrenal glands to secrete cortisol. For drugs (such as mitotane) and diseases (such as immune mediated hypoadrenocorticism) that cause permanent effects on the adrenal gland the ACTH stimulation test provides an effective method of monitoring the adrenal gland. However due to the relatively short lasting effects of trilostane the ACTH stimulation test varies considerably with the time of testing relative to dosing [24]. Early studies of trilostane were often conducted without the knowledge of later studies and so the clinical effects were sometimes discordant to the ACTH stimulation test results. The short duration of action of trilostane may have a protective effect against the development of hypoadrenocorticism, as many dogs with no serum cortisol response to ACTH stimulation 2 – 3 hours post trilostane dosing, do not develop signs of hypoadrenocorticism [19]**.** However equally many dogs that have a target level post ACTH stimulation test serum cortisol will exhibit signs of HAC [20, 24]. Various different timings and cortisol target levels for the ACTH stimulation test when used to monitor trilostane therapy have been used [18-23]. The lower the target range the greater the chance of hypoadrenocorticism. However in the earlier studies many dogs did not have their cortisol levels reduced to the authors stated target range [18-21]. Later studies, which tended to be more precise on the timing of the ACTH stimulation test, achieved a higher rate of success in this respect [22, 23].

Based on the data in Table 1, the author's currently recommended target range for the post ACTH cortisol concentration is 40 to 120 nmol/l (1.4–4.3 mg/dl) for ACTH stimulation tests started 2 to 4 hours after dosing; however if dogs have a post-ACTH cortisol concentration of 120–200 (4.3-7.2 mg/dl) and are responding well to treatment then an increase in monitoring

rather than dose may be more acceptable to the owners. Other methods of monitoring trilostane are under active investigation and are considered below.

Dose changes

Most of the published studies on trilostane treatment record details of the number of dose changes. To some extent this has to be interpreted in the light of the starting dose and the target range for post ACTH cortisol concentrations in an individual study. However in all studies a sizeable proportion of dogs required a dose increase and a small minority required a dose decrease. These results emphasise the importance of regular monitoring when treating a case of canine HAC. Even once stable dogs may become unstable at subsequent monitoring visits.

Efficacy and Survival

In the studies in Table 1 trilostane it was found to be between 67 to 100% effective in resolving the various signs of HAC over 3 to 6 months [18-23]. In contrast, mitotane is effective in about 80% of cases of PDH [27]. It is reasonable to conclude that trilostane is at least as effective as mitotane in controlling the clinical signs of most cases of canine HAC.

There have been two studies that have compared the survival times of dogs treated with trilostane with those treated with mitotane [25,26]. In the first study the survival times of 148 dogs treated for PDH were studied using clinical records from three UK veterinary centers [25]. Of these animals 123 (83.1%) were treated with trilostane, while 25 (16.9%) were treated with mitotane. The median survival time for animals treated with trilostane was 662 days (range 8-1971) and for mitotane it was 708 days (range 33-1339). There was no significant difference between the survival times for animals treated with trilostane and those treated with mitotane (see Figure 1).

In the second study the median survival time of forty dogs treated with trilostane twice a day (900 days) was significantly longer (P=0·05) than the median survival time (720 days) of 46 dogs treated with mitotane using a non-selective adrenocorticolytic protocol [26]. Both protocols had similar levels of long term efficacy (75%), although short term efficacy with the mitotane was higher. They also had a similar prevalence of side effects (25%), although two of the mitotane treated dogs died. This prevalence of side effects with trilostane has not been recorded by others [18-23]. In those countries which do not currently regard either routine twice daily dosing with trilostane or non-selective adrenocorticolysis with mitotane as first

choice protocols this study has more relevance to animals that have failed a conventional first choice protocol.

Safety (to humans)

Trilostane does not require any special safety precautions in its handling. It is formulated in capsules that are now available in a range of sizes (therefore splitting or re-formulating capsules should not be necessary). If a capsule is accidentally damaged the drug does not cross the skin barrier. Ingestion or inhalation of small quantities of trilostane would be expected to have no effect on a human being. If taken in large doses (which would have to be a deliberate action) then trilostane can act as an abortifacent and potentially could induce hypocortisolism. Doses of 60mg or more given 4 times daily over 4 weeks were used in ten healthy men with minimal effects on their adrenal function [28]. In contrast the risks of handling mitotane are well documented [29]. Trilostane is safer for humans to handle than mitotane.

Safety and adverse effects in dogs

One common feature of the studies in Table 1 is that trilostane appears to be well tolerated by almost all dogs. If the numbers of dogs from these 6 clinical trials are combined then only 39 dogs out of 244 dogs (16%) treated with trilostane developed adverse effects which may have been attributable to trilostane [18-23]. This prevalence of side effects compares favourably with those reported with mitotane (25 to 42%) [27, 30, 31].

If failure to respond is regarded as an adverse effect then it is probably the most common adverse effect of trilostane administration. In these cases an increase in the dose (and /or frequency) or a change to an alternative medication (such as mitotane) is indicated. More serious side effects include (in order of severity) adrenal necrosis, hypoadrenocorticism, hyperkalaemia and a few others. These are described below.

Adrenal necrosis and hypoadrenocorticism

The most serious side effect of trilostane that has been identified to date is acute adrenal necrosis. This has been documented in 2 case reports, one fatal and the other requiring permanent glucocorticoid therapy [32, 33]. It may also have been the cause of sudden death and sudden decreases in trilostane requirement in a few other cases [16]. Necrosis of the adrenal cortex can not be directly explained by the competitive inhibition of steriodogenesis. However adrenal necrosis also cannot be dismissed as isolated idiosyncratic reactions.

Varying degrees of adrenal necrosis and associated inflammation have been described in 5 out of 7 non-randomly selected post mortems of dogs that had been treated with trilostane [34]. All 7 dogs showed some degree of adrenal hyperplasia as well. In 2 of the dogs the lesions were sufficiently severe that they could have been associated with hypoadrenocorticism, however both cases had also received mitotane. In both cases and in 4 of the other dogs other causes of death were also definitively established. The severity of the lesions may have been related to the doses of trilostane used and the duration of treatment [34]. The interference from this study is that adrenal hyperplasia is common in trilostane treated dogs but it may also be associated with a low grade adrenal necrosis.

The development of adrenal necrosis could be due to the hypersecretion of ACTH [34]. It has been demonstrated that trilostane causes an increase in ACTH concentrations [35]. This leads to the increase in the size of the adrenal glands that is observed in many dogs that are treated with trilostane [36]. Moreover it has been shown that even short periods of administration of ACTH can also, paradoxically, result in degeneration, focal necrosis and haemorrhage of human adrenal glands [37].

Adrenal necrosis does not explain most of the cases of hypoadrenocorticism seen in trilostane treated dogs. Most cases of hypoadrenocorticism associated with trilostane recover rapidly following temporary cessation of the drug but continue to require the drug to control the clinical signs. This suggests that these cases have suffered from over dosage rather than adrenal necrosis [18-23]. Most affected cases have typical electrolyte changes (hyponatremia, hyperkalemia) typical of hypoadrenocorticism. However one case has been described which developed isolated hypocortisolism [33]

There is also a theoretical risk that trilostane-induced adrenal hyperplasia could develop into adrenal tumours [34]. However no evidence for this has been published.

ACTH concentrations also increase in normal dogs that are treated with trilostane [38] . This is associated with an increase in pituitary size (as assessed by MRI) and histological evidence of pituitary corticotroph hyperplasia and bilateral adrenal hyperplasia. It seems reasonable to assume that trilostane could result in an increase in the size of pituitary tumours but again no evidence for this has been published.

Hyperkalaemia

Two of the 6 clinical studies in Table 1 recorded a mild increase in median serum potassium concentrations [19,21] . Dogs that develop hyperkalemia do not appear to have a low aldosterone concentration (Ramsey and Neiger, unpublished observations). The mechanism of action of this hyperkalemia has not been identified. Any trilostane treated dog with a mild increase in potassium should be checked with an ACTH stimulation test, rather than empirically reducing the dose. Trilostane can then be safely withheld whilst waiting for the results of the test.

Other side effects

Trilostane is associated with vomiting and diarrhoea in some dogs independently of any effects on cortisol levels. Successful treatment with trilostane might also lead to the development of previously suppressed immune mediated, inflammatory or neoplastic diseases however, so far, there have been no reports of these side effects. All of these are well described in relation to the use of mitotane and readers are referred to standard texts for descriptions of these side effects [27].

Use in PDH dogs with concurrent conditions

Manufacturers recommend that trilostane should not be used in animals suffering from primary hepatic disease and/or renal insufficiency. However the basis for this recommendation is unclear in the published literature. It is true to say that information is not available on what dosage adjustment should be made in dogs with primary hepatic disease and/or renal insufficiency. Similarly there are no studies looking at trilostane use in dogs with concurrent diabetes mellitus and HAC. Currently the author does not reduce the dose of trilostane when treating a dog with diabetes and HAC. It seems logical to give the trilostane and insulin at the same frequency (i.e. either both once a day or both twice a day).

Use in canine adrenal dependent hyperadrenocorticism

There have been no large scale studies of the treatment of adrenal dependent HAC (ADH) in dogs. However trilostane does appear to work in ADH. Evidence of efficacy is provided by one small series and a couple of case reports [39-41]. It is not known if the dose, frequency or monitoring of trilostane treatment in ADH cases should be the same as PDH cases or not. Until more data is available it would be prudent to exercise caution when using trilostane in such cases.

Effects on other endocrine parameters

Aldosterone

Aldosterone secretion in dogs with untreated HAC is generally considered to be decreased [42, 43]. The effect of trilostane on aldosterone in dogs with HAC has been reported in 3 studies. One study of 15 dogs suggested an increase in basal plasma aldosterone concentrations (PAC) with trilostane treatment [12]. In 2 other studies (of 17 and 63 dogs) trilostane did not appear to have a significant effect on basal plasma aldosterone concentrations [23, 44]. Trilostane does appear to reduce ACTH stimulated aldosterone concentrations in dogs with HAC [12, 44]. A reduction in both basal and ACTH stimulated aldosterone concentrations is also seen in mitotane treated dogs [42, 43]. In all 3 of the trilostane studies the observed effects on aldosterone concentrations were less pronounced than the effects on cortisol concentrations.
In humans, and it is suggested in dogs, plasma rennin activity (PRA) (and specifically the PRA:PAC ratio) are a better indicator of mineralocorticoid deficiency than PAC alone [23]. It has been shown in a series of 63 dogs that PRA is increased by, and the PRA:PAC ratio is reduced by, trilostane therapy [23].

Effect on urinary corticoid: creatinine ratio

If the ACTH stimulation test only provides a measure of the short term effects on trilostane then there is a need to identify a test that measures the long term control of HAC. Initially it would appear that the urinary corticoid: creatinine ratio (UCCR) makes a logical choice. However an early study reported that it was not useful, although few details were given [19]. Another early study demonstrated that the mean UCCR did not decrease significantly with trilostane treatment [20]. These authors did however note that the UCCR was lower when the urine was collected shortly after dosing and higher when collected later. These authors felt that UCCR was useful for assessing the duration of effect of trilostane when collected 24 hours after dosing when it was having least effect. However overall correlation with ACTH stimulation test results and clinical improvement was low in this study [20]. In a recent prospective study of 18 dogs that had been successfully treated with once daily trilostane UCCRs were monitored every 2 weeks for at least 8 weeks [45]. Although UCCRs did decrease compared with pre-treatment values they did not fall to below the upper limit of the reference range in the majority of dogs. Moreover, the UCCRs of 11 dogs that initially had insufficient doses of trilostane did not differ significantly from when the dosage was optimal. Post-ACTH cortisol concentrations did not correlate significantly with UCCRs at rechecks

during trilostane treatment. However UCCR could identify dogs that were being over-treated with trilostane with greater success. These results are similar to those achieved with mitotane [46-48].

However another recent study using twice daily trilostane suggested that measuring UCCR in a urine sample collected at home the same morning as a post-dosing ACTH stimulation test was carried out provided useful data with regards to the duration of effect of the trilostane [22]. In many respects this replaces a second (pre dosing) ACTH stimulation test being carried out in dogs that had failed to respond to once daily dosing as described by others [24]. Further research is needed to confirm these findings.

Effect on haptoglobin and other acute phase proteins

Glucocortiocids have been demonstrated to cause a significant increase in haptoglobin concentrations and haptoglobin has been assessed as a marker for good control of HAC with trilostane [49]. It was found that although serum haptoglobin concentrations decreased with trilostane therapy the concentrations did not closely relate to the degree of control of HAC as assessed by an ACTH stimulation test. A further study demonstrated that haptoglobin measurements, even when combined with other parameters such as cholesterol an/ or alkaline phosphatase, were only moderately informative of disease control. The study also demonstrated that serum amyloid A but not C-reactive protein decreased with trilostane therapy [50].

Effect on thyroid and parathyroid hormones

Hyperadrenocorticism is associated with a reduction in thyroxine [51]. Fourteen out of 20 dogs demonstrated an increase in thyroxine following trilostane treatment however, although the mean concentration increased, this increase was not found to be significant [52]. In contrast there was a significant increase in the mean concentrations of thyroid stimulating hormone with 14 out of the 20 dogs demonstrating an increase (of these 14 dogs, 10 also showed an increase in thyroxine concentrations). There was a significant decrease in the mean free thyroxine concentration (although most of the treated dogs had concentrations that were within the reference range).

Hyperadrenocorticism is also associated with an increase in parathyroid hormone concentrations, which can be regarded as adrenal secondary hyperparathyroidism [53]. Trilostane treatment has also been shown to cause a decrease in parathyroid hormone concentrations although many dogs do not return to normal [54].

Other uses of trilostane in dogs

Trilostane has been demonstrated to be effective in the treatment of alopecia X of Pomeranians, poodles and Alaskan malamutes which many authorities consider it to be a mild, slowly progressive form of pituitary dependent HAC [55, 56]. The doses used in these two studies were different (9 to 11 mg/kg once daily for the Pomeranians and Miniature poodles, 3.0 to 3.6 mg/kg once daily for the Alaskan malamutes). Two of the Pomeranians did not respond to this dose but did respond when the dose was increased by doubling the frequency of administration to twice daily [55]. The efficacy of trilostane in alopecia X is in marked contrast to the inconsistent and often temporary results achieved with other therapies such as melatonin, thyroxine and sex hormones. As the condition does not usually progress rapidly or cause significant other effects (such as polyuria, polyphagia) the need for, and risks of, therapy should be carefully discussed with owners before starting trilostane.
In humans trilostane has been used to treat human hyperaldosteronism [6]. Although the effects of trilostane on aldosterone are less than on cortisol it would be possible to contemplate the use of trilostane in a case of canine or feline hyperaldosteronism (Conn's syndrome) particularly when aldosterone antagonists such as spironolactone have not been effective.

Trilostane in hyperadrenocorticism in other species

The use of trilostane has been reported in the treatment of cats, horses and guinea pigs with hyperadrenocorticism [57-60]. The drug appears to have similar effects to those described in dogs however data is limited and caution is advisable. In addition there is one case report of its use in a cat with bilateral adrenal enlargement and excessive sex steroid hormone production [61].

Summary and future studies

The introduction of trilostane has increased the options for the management of canine hyperadrenocorticism in many countries. The drug is safer for humans to handle than mitotane; it is nearly as effective as mitotane and has a lower frequency of serious adverse reactions.

The optimal dosing interval has still to be formally determined. Studies comparing the success of once daily with twice daily administration will be important. Whatever the starting dose

and frequency, trilostane therapy still requires careful monitoring. However the ACTH stimulation test may be a suboptimal method to be the sole assessment of the efficacy and safety of trilostane. Although to date, no better method has been identified, it is important that further studies are undertaken on the UCCR and other measurements of total daily cortisol production. The long term frequency of such monitoring should also be properly assessed.

Trilostane does not cure hyperadrenocorticism and some cases are not well controlled by it. In these poorly controlled cases other therapeutic options (specifically mitotane) are indicated. Therefore access to, and the skills required to use, mitotane still need to be maintained within the veterinary profession.

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Diagram 1

Biosynthetic pathways in steriodogenesis. Different tissues of the adrenal gland express different enzymes so not all processes occur in all cells. The principle target for the competitive inhibitor trilostane is 3β hydroxysteroid dehydrogenase (3β HSD).

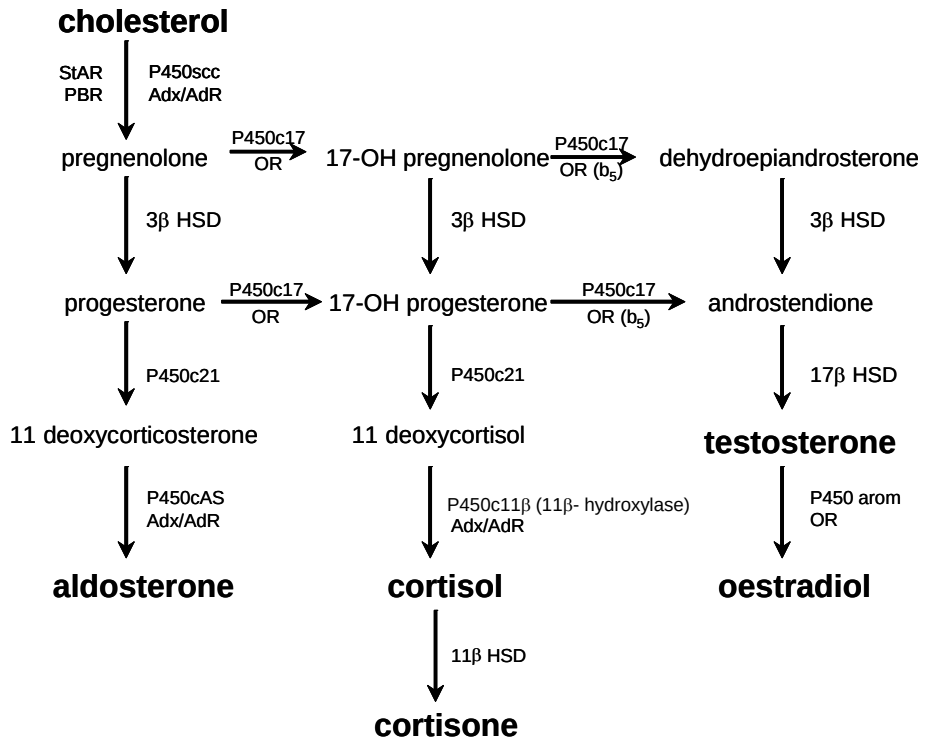

Figure 1. Kaplan Meier Survival Curve for both mitotane and trilostane treated animals. Dogs alive at the completion of the study and those lost to follow up were censored (indicated by a vertical line). Figure reproduced with permission [25].

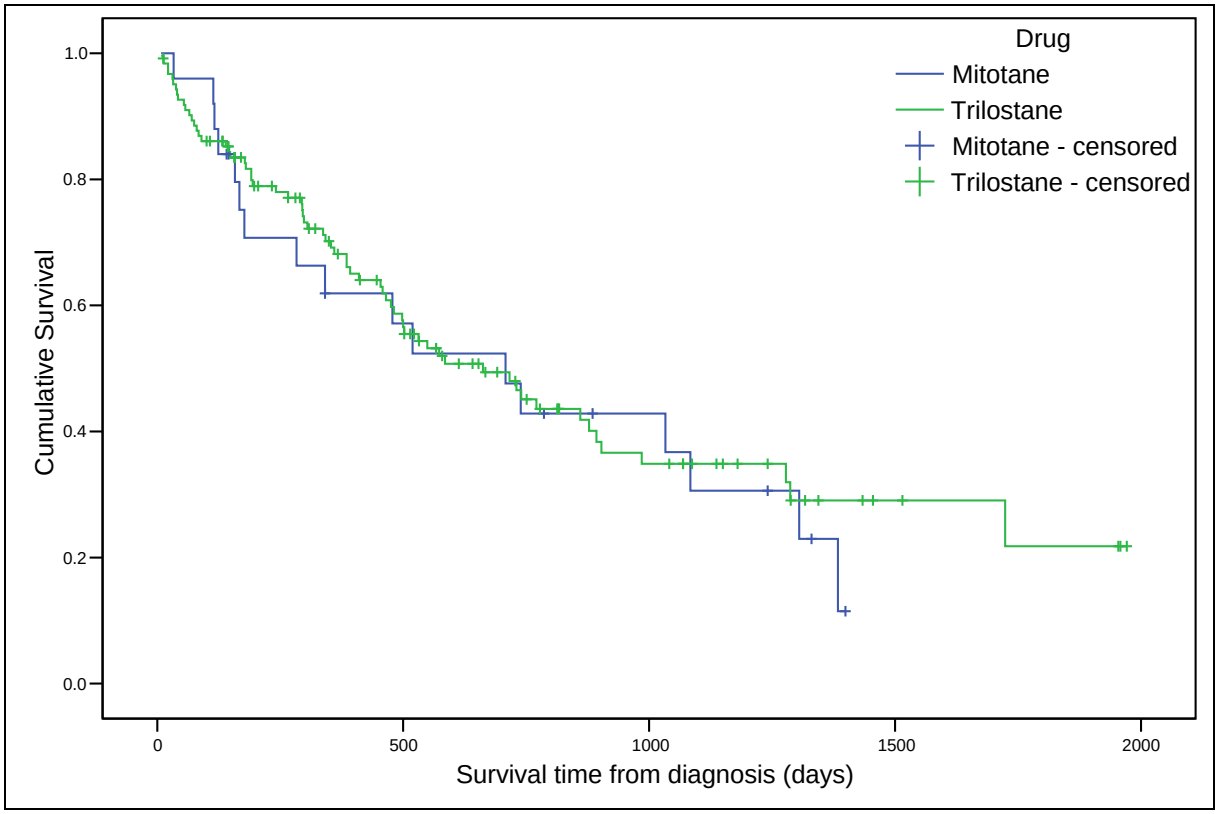

Table 1 Summary of 6 clinical studies on the use of trilostane in canine hyperadrenocorticism

Reference	[18]	[19]	[20]	[21]	[22]	[23]
Country	UK	Switzerland	Australia	Spain	USA	Netherlands
Study design						
PDH dogs	78	11	30	44	18	63
ADH dogs	0	0	0	0	4	0
Starting dose	Mean 5.9 mg/kg q24h Range 1.8 to 20	Median 6.3 mg/kg q24h Range 3.9 to 9.2	Median NS Range 3 to 12	Mean 3.1 mg/kg q12h (S.D. = 1.3)	Median 1.4 mg/kg q12h Range 0.5 to 2.5	Median NS Range 2-4 mg/kg q24h
Monitoring	10d, 4, 12, 24w, then every 12-24w	1,3- 4, 6-7, 12-16, 24-28w	10, 30, 90, 180d	7d, 1, 3, 6 months, then every 6 months	1-2, 4-8, 8 -16 w	3w, then every 3w until stable
Target cortisol range	20-250 nmol/l	27-69 nmol/l	25-125 nmol/l	27-135 nmol/l	<150 nmol/l	30-190 nmol/l
Time of sampling	"Most within a few hours"	2 to 6 hours	No particular time	4 to 6 hours at 7d, then 8 to 12 hours	3 to 4 hours	2 to 4 hours
Tablets given with food	Unknown	Unknown	Unknown	NS	Yes	NS
Length of follow up	Up to 4 years, 30 dogs for more than 24 w	7 dogs for 1 year, 3 dogs for 2 years	Mean 384 days, range 170 - 600 days	Up to 3.5 years	16 weeks	Up to 12 weeks
Study Results						
Dose changes	23 increased and 9 decreased during study	4 increased and 3 decreased during study	NS	10 increased and 2 decreased at 1 month	10 increased 4-8 weeks 5 increased 8-16 weeks	22 increased and 4 decreased during study
Withdrawals	None	None	None	5 dogs ("economic reasons")	6 dogs (4 had surgery for ADH)	None
Final dose	Mean 7.3mg/kg q24h Range 1.6-27.2 mg/kg *	Median 6.1 mg/kg q24h Range 4.1-15.6 mg/kg	Median 16.7 mg/kg q24h Range 5-50 mg/kg	Mean 3.2 mg/kg q12h	Mean 1.7 mg/kg q12h Range 1.1-2.8 mg/kg	Mean 2.8 mg/kg q24h Range 0.8-5.8 mg/kg
Clinical efficacy	60 (77%) improved by 4 weeks. 24/39 dogs with alopecia improved	9 (82%) improved after 6 months of treatment	30 (100%) improved at 90 days	20 stable and improved out of 30 (67%) at 6 months	15 improved at 4–8 weeks, 16/18 (89%) at 8-16 weeks	60 (95%) improved
Dogs in target cortisol range	59 (76%) at some time during study	Median above target range at 4 re-evaluations	17 (57%) at 90 days, 23 (out of 29 (79%) at 180 days	26 out of 36 (72%) at 3 months	14 out of 16 (87%) at 8-16 weeks	100% (definition of inclusion)
Adverse effects	2 dogs died early on hypoAC in 2 dogs (1 died). 13 other minor adverse events	2 minor adverse events	One died (unrelated cause). No others in first 6 months, later 4 cases of hypoAC	hypoAC in 11 (25%)	hypoAC in 2 dogs	hypoAC in 5 dogs, 3 during the study and 2 after study completed
Other comments	*Figures not in paper but provided by authors from original data		5 dogs had failed other treatments before start of study	Mean survival time 31 months (95% CI = 26 to 36)	3 dogs treated q8h	

Key d = days, w = weeks, NS = not stated in paper