



**University of  
Zurich**<sup>UZH</sup>

**Zurich Open Repository and  
Archive**

University of Zurich  
Main Library  
Strickhofstrasse 39  
CH-8057 Zurich  
[www.zora.uzh.ch](http://www.zora.uzh.ch)

---

Year: 2014

---

## Trilostane - the good and the bad

Reusch, Claudia E

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-100006>

Conference or Workshop Item

Originally published at:

Reusch, Claudia E (2014). Trilostane - the good and the bad. In: WSAVA Congress, Cape Town, South Africa, 16 September 2014 - 19 September 2014.

The standard medical treatment for HAC (PDH and ATH) dogs has long been mitotane. Mitotane leads to selective necrosis of the adrenal cortex, which may be partially or completely destroyed, depending on the treatment protocol. The efficacy of mitotane is favourable and more than 80% of dogs with PDH have a good to excellent response. Disadvantages of mitotane include potential development of adrenocortical insufficiency, possible drug intolerance, and a relatively high frequency of relapses during therapy. The first report of the use of trilostane was by Hurley et al in 1998, who successfully treated 13 dogs with PDH and 2 with ATH. Since then, the drug has gained wide popularity and is now licensed for the use in dogs under the name of Vetoryl®. Various clinical trials have shown that trilostane is an efficacious drug and that the majority of dogs with HAC show good clinical response. If used cautiously (e.g. low starting dose and close monitoring), side effects are rare. However, many questions on the exact mode of action, optimal dose regimen and monitoring protocol are still unanswered. It is also not known, why some dogs show poor clinical response despite tight control of the adrenal function and why dose requirements vary tremendously.

From studies in humans and various other species it is known that trilostane is a competitive inhibitor of 3 $\beta$ -hydroxysteroid-dehydrogenase. This enzyme system mediates the conversion of pregnenolone to progesterone in the adrenal gland. Cortisol, aldosterone and androstendione are produced from progesterone via various biochemical pathways. Since trilostane inhibits progesterone synthesis, it blocks the synthesis of its end products. Recently, it was shown that also in dogs, trilostane has an inhibitory effect on the 3 $\beta$ -hydroxysteroid dehydrogenase enzyme system. Surprisingly, studies revealed additional effects more distal in the enzyme cascade, most likely on the 11 $\beta$ -hydroxylase and possibly on the 11 $\beta$ -hydroxysteroid dehydrogenase. It has also been shown that trilostane influences the interconversion of active cortisol to inactive cortisone, either directly or indirectly, leading to a reduced cortisol to cortisone ratio. Trilostane may also have an effect on the intracellular glucocorticoid receptors; in rats it was shown that glucocorticoid mRNA were significantly decreased by trilostane. After absorption, trilostane has to be converted to active metabolites, such as ketotrilostane in the liver, a process which has not been thoroughly studied in dogs. The multitude of effects, which may not be equally active in all dogs, most likely is one of the reasons for the variable clinical response in dogs treated with trilostane.

Another potential reason is the variability in plasma levels of trilostane which may be due to low water solubility and inconsistent absorption. Feeding increases the absorption of the drug. Peak plasma concentrations of trilostane are generally seen after 1.5 – 2 hours and return to baseline levels is after 10 – 18 hours. Consequently, results of the ACTH stimulation test vary considerably depending on the time of testing after drug administration. A recent study demonstrated that post-ACTH cortisol levels were significantly higher when the ACTH test was started 4 hours after administration of trilostane compared to a start after 2 hours.

Trilostane not only lowers the cortisol concentration, but also the aldosterone concentration. The decrease of aldosterone, however, is considerably less than that of cortisol. Although some dogs with HAC show mild hyperkalemia, there is no correlation between potassium and aldosterone concentrations.

Adverse effects are seen in 10 – 25% of dogs and are often mild (e.g. GI signs) and self-limiting. In some dogs, however, hypoadrenocorticism may develop requiring withdrawal of the drug and possibly symptomatic treatment (IV fluids, glucocorticoids). Hypoadrenocorticism may be short-lived and due to an overdose of trilostane. It may, however, also be caused by adrenal necrosis leading to long-lasting or permanent adrenal insufficiency and even to death. One of our recent studies suggests, that adrenal necrosis is not due to a direct effect of trilostane, but is caused by the increase of endogenous ACTH. Synthesis of endogenous ACTH increases substantially during treatment with trilostane due to the lack of negative feedback. In our hospital, adrenal necrosis has become a very rare event since we use low dosages based on kg body weight.

Over the years, treatment protocols have changed considerably and there are currently no widely accepted guidelines.

During the initial years, trilostane dose was based on the available capsule size of 30 mg and 3

categories of bodyweight: 30 mg (1/2 capsule) SID for dogs < 5 kg, 60 mg SID for dogs 5-20 kg, and 120 mg SID for dogs > 20 kg. Today 10mg, 30 mg, 60 mg and 120 mg capsules are commercially available. Re-formulation by a pharmacist may provide additional sizes (e.g. 5 mg, 2.5 mg). In 2006, endocrinologists of seven European countries suggested in a consensus statement that initial dose should be according to bodyweight and should be in the range of 2 – 5 mg/kg (in dogs  $\leq$  10 kg at the lower end of the dose range). Applications should be SID, in the morning with food. Re-evaluations should be performed after 1-2 weeks, 4 weeks, 12 weeks and then every 3 months including history, physical examination, the most important blood parameters (kidney parameters, liver enzymes, electrolytes) and an ACTH stimulation test. The latter test should be performed 2 to 3 hours after trilostane administration, which corresponds to its peak effect. The target range of the post ACTH cortisol level at 2-3 hours post pill should be 40 to 150 nmol/l (1.4 – 5.4  $\mu$ g/dl). Adjustments of trilostane dose should be made in increments of 10 to 30 mg/dog. Some time after those recommendations, it was in fact shown that dosing per kg body weight is associated with less side effects compared to dosing according to weight categories. Recently, it became obvious, that even lower doses are efficacious to control the disease. Various authors have recently suggested using BID instead of SID administration. BID administration may lead to a slightly faster control of the disease and possibly increases the number of dogs with good clinical response. However, the need of BID administration may have a negative impact on owner compliance. In our hospital, we amended the protocol various times during the last 15 years. The main changes were reductions of initial trilostane doses. We currently start trilostane therapy with a dose of 1 (- 1.5) mg/kg SID and ask the owner to administer the drug in the morning with the same type and amount of food. In large dogs (> 20 kg), usually less than 1 mg/kg SID is given (e.g. a 30 kg dog receives 20 mg, a 40 kg dog 30 mg SID). Re-evaluations are scheduled after 2, 4, 8, 12 - 16 weeks and every 4 - 6 months thereafter. Besides clinical signs, the post-ACTH cortisol concentration is used to amend the dose. The ACTH test is performed 2 – 3 hours after trilostane administration and our post-ACTH cortisol target is 54 – 135 nmol/l (2 – 5  $\mu$ g/dl). After 8 – 12 weeks we evaluate, if SID application is adequate by performing an ACTH test 24 hours after the last trilostane administration. If post-ACTH cortisol concentrations are above approximately 200 nmol/l (7.5  $\mu$ g/dl), application frequency is switched to BID. In dogs with diabetes mellitus and HAC, trilostane is administered BID from the beginning. The majority of dogs is well controlled with SID application, some dogs, however, benefit from a switch to BID therapy.

## References

- Arenas C, Melián C, Pérez-Alenza MD. Evaluation of 2 trilostane protocols for the treatment of canine pituitary-dependent hyperadrenocorticism: twice daily versus once daily. *J Vet Intern Med.* 2013;27(6):1478-1485.
- Augusto M, Burden A, Neiger R, Ramsey I. A comparison of once and twice daily administration of trilostane to dogs with hyperadrenocorticism. *Tierarztl Prax Ausg K Kleintiere Heimtiere* 2012;40(6):415-424.
- Bonadio CM, Feldman EC, Cohen TA, Kass PH. Comparison of adrenocorticotrophic hormone stimulation test results started 2 versus 4 hours after trilostane administration in dogs with naturally occurring hyperadrenocorticism. *J Vet Intern Med.* 2014 (Epub ahead of print).
- Burkhardt WA, Guscelli F, Boretti FS, Ivos Todesco A, Aldajarov N, Lutz TA, Reusch CE, Sieber-Ruckstuhl NS. Adrenocorticotrophic hormone, but not trilostane, causes severe adrenal hemorrhage, vacuolization, and apoptosis in rats. *Domest Anim Endocrinol* 2011;40(3):155-164.
- Feldman EC, Kass PH. Trilostane dose versus body weight in the treatment of naturally occurring pituitary-dependent hyperadrenocorticism in dogs. *J Vet Intern Med.* 2012;26(4):1078-1080.
- Malouitre SD, Barker S, Puddefoot JR, Jalili J, Glover HR, Vinson GP. Regulation of hepatic steroid receptors and enzymes by the 3 $\beta$ -hydroxysteroid dehydrogenase inhibitor trilostane. *J Steroid Biochem Mol Biol.* 2006;101(2-3):97-105.

Reusch CE, Sieber-Ruckstuhl N, Wenger M, Lutz H, Perren A, Propischil A. Histological evaluation of the adrenal glands of seven dogs with hyperadrenocorticism treated with trilostane. *Vet Rec.* 2007;160(7):219-24.

Sieber-Ruckstuhl NS, Boretti FS, Wenger M, Maser-Gluth C, Reusch C. Cortisol, aldosterone, cortisol precursor, androgen and endogenous ACTH concentrations in dogs with pituitary-dependent hyperadrenocorticism treated with trilostane. *Domest Anim Endocrinol.* 2006;31(1):63-75.

Sieber-Ruckstuhl NS, Boretti FS, Wenger M, Maser-Gluth C, Reusch CE. Serum concentrations of cortisol and cortisone in healthy dogs and dogs with pituitary-dependent hyperadrenocorticism treated with trilostane. *Vet Rec.* 2008;163(16):477-81.

Teshima T, Matsumoto H, Kumagai T, Kurano M. Expression of 11 $\beta$ -hydroxysteroid dehydrogenase isoforms in canine adrenal glands treated with trilostane. *Vet J.* 2014;200:452-455.

Wenger M, Sieber-Ruckstuhl NS, Müller C, Reusch CE. Effect of trilostane on serum concentrations of aldosterone, cortisol, and potassium in dogs with pituitary-dependent hyperadrenocorticism. *Am J Vet Res.* 2004;65(9):1245-1250.