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Original Article

Incidence and risk factors for hypoadrenocorticism in dogs treated with trilostane

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ABSTRACT

The aim of this study was to describe the incidence and permanence of hypoadrenocorticism associated with trilostane treatment and to assess potential risk factors for hypoadrenocorticism. A retrospective cohort study was conducted using case records for 156 dogs treated with trilostane after a diagnosis of hyperadrenocorticism. Occurrences of hypoadrenocorticism were categorised as either transient or permanent. After initiation of treatment with trilostane, the estimated cumulative incidence of hypoadrenocorticism was 15% by 2 years and 26% by 4.3 years, respectively. Occurrences of hypoadrenocorticism were transient in 14/19 (74%) affected study dogs. The risk of hypoadrenocorticism was not significantly associated with trilostane dose rate and other potential risk factors assessed were not significantly associated with subhazard of hypoadrenocorticism, but effect estimates for most were imprecise. In conclusion, approximately 15% of dogs being treated with trilostane developed hypoadrenocorticism within the first 2 years of treatment and about one quarter became affected by 4 years. However, first occurrences of hypoadrenocorticism were mostly transient. Over the range of dose rates studied, each 1 mg/kg/day increase in trilostane dose rate resulted in, at most, only a small increase in the risk of developing hypoadrenocorticism.

Introduction

Trilostane is a synthetic steroid analogue that competitively inhibits 3-β-hydroxysteroid dehydrogenase and reversibly inhibits its conversion of progesterone to pregnenolone (Braddock et al., 2003). It also inhibits 11-β-hydroxylase and 11-β-hydroxysteroid dehydrogenase (Sieber-Ruckstuhl et al., 2008). This results in reduced production of glucocorticoids and, to a lesser extent, mineralocorticoids and androgens. Hypoadrenocorticism may result from over-suppression of cortisol and/or mineralocorticoid production (Neiger et al., 2002; Braddock et al., 2003). In most dogs, hypoadrenocorticism resolves once trilostane is withdrawn, but iatrogenic permanent hypoadrenocorticism has been reported (Chapman et al., 2004; Ramsey et al., 2008; Gojska-Zygnar et al., 2011). Permanent hypoadrenocorticism may be the result of adrenocortical necrosis. While the reason for this in dogs is unknown, in rats, adrenocorticotropic hormone (ACTH), and not trilostane, has been suggested as the cause (Burkhardt et al., 2014).

Risk factors for trilostane-related hypoadrenocorticism have not been defined. It has been suggested that low dose rates of trilostane may reduce the incidence of hypoadrenocorticism compared to higher dose rates (Feldman, 2011). Also, there is some evidence that heavier dogs may be more sensitive to trilostane (Braddock et al., 2003; Foster, 2011; Feldman and Kass, 2012). However, this refers to clinical responsiveness to trilostane and not necessarily to risk of hypoadrenocorticism.

In order to document the frequency of trilostane-related hypoadrenocorticism in dogs with hyperadrenocorticism, we conducted an observational study and analysed whether these occurrences were transient or long term, and assessed potential risk factors for hypoadrenocorticism. We hypothesised that the risk of trilostane-related hypoadrenocorticism increases with trilostane dose rate and body weight.

Materials and methods

Study overview

We conducted a retrospective, single cohort study using clinical records for all dogs presented to Veterinary Specialist Services, Queensland, from January 2003 to

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December 2015. All dogs treated with trilostane (Vetoryl, Dechra[1]) or compounded trilostane were included if: (1) they met our case definition of hyperadrenocorticism; (2) had at least two ACTH stimulation tests following initiation of trilostane treatment; and (3) were not treated with adrenalectomy or mitotane before or after trilostane treatment. Trilostane dose rates (mg/kg/day) were calculated using body weights at the time of commencement of trilostane and any subsequent recorded body weights.

Diagnosis of hyperadrenocorticism

Dogs were diagnosed with hyperadrenocorticism if they had at least two clinical signs (polyuria/polydipsia, polyphagia, alopecia, pot-belly, panting, coat and/or skin changes) and a positive result on a supportive provocative test. Low dose dexamethasone suppression test (LDDST) results ≥38 nmol/L at 8 h and ACTH stimulation tests with a post-stimulation cortisol concentration ≥600 nmol/L were considered to be positive. Dogs included in the study were treated with trilostane only after significant co-morbid diseases (e.g. neoplasia, diabetic ketoacidosis) had been controlled. Dogs with azotaemia were included, but all dogs with values available for review were classified as either normal or International Renal Interest Society (IRIS) stage 1 or 2 at the time of diagnosis of hyperadrenocorticism. No dogs for which values were available were classified as IRIS stage 3 and 4, respectively.

Case definition of hypoadrenocorticism

The outcome of interest was the first occurrence of hypoadrenocorticism after commencement of trilostane. Criteria for hypoadrenocorticism were an ACTH stimulation test compatible with hypoadrenocorticism (post-stimulation cortisol concentration ≤40 nmol/L at 4–6 h post-trilostane administration) and at least two concurrent clinical signs (vomiting, diarrhoea, weight loss, inappetence, lethargy, weakness and/or collapse) that were not clearly attributable to another disease process (e.g. diabetic ketoacidosis, neoplasia) except azotaemia. Azotaemia was not excluded, since it is a common clinical finding in naturally occurring hypoadrenocorticism (van Lanen and Sande, 2014). No dogs were receiving corticosteroids at the time of ACTH stimulation testing. The onset of hypoadrenocorticism was set as the date at which a dog had a compatible ACTH stimulation test result and concurrent clinical signs of hypoadrenocorticism.

Classification of hypoadrenocorticism permanency

The first occurrences of hypoadrenocorticism were classified as permanent or transient. Dogs were diagnosed with permanent hypoadrenocorticism if they had a period of at least 6 months following the diagnosis of hypoadrenocorticism during which time they had at least one ACTH stimulation test that was consistent with hypoadrenocorticism following a brief period of discontinuation of glucocorticoids. Dogs were classified as having transient hypoadrenocorticism if they had ACTH stimulation test results documenting a post-stimulation cortisol concentration of ≥40 nmol/L or a return of clinical signs compatible with hyperadrenocorticism (while not receiving glucocorticoids) at any stage following diagnosis of hypoadrenocorticism. Hypoadrenocorticism permanency could not be classified if the dog died, was euthanased, or was lost to follow up within 6 months of first diagnosis of hypoadrenocorticism.

Anatomical localisation of the cause of hyperadrenocorticism

Hyperadrenocorticism was classified as pituitary-dependent (PDH) or adrenal-dependent (ADH) at the time of initial diagnosis. PDH was diagnosed on the basis of a supportive LDDST, computed tomography (CT), magnetic resonance imaging (MRI), ultrasonography or endogenous ACTH assay. Imaging criteria for diagnosis of PDH and ADH were taken from previously published guidelines (Benchekroun et al., 2010; Behrend et al., 2012). The possibility of concurrent PDH and ADH or bilateral adrenal tumours could not be excluded in some cases categorised as either PDH or ADH.

Follow-up and statistical analysis

Times from the commencement of trilostane treatment until the first diagnosis of hypoadrenocorticism were assessed using survival analysis models, fitted using Stata (version 14.1, StataCorp). Dogs that were not diagnosed with hypoadrenocorticism were right censored on their date of last follow-up. For dogs that died or were euthanased during the follow-up period and were not diagnosed with hypoadrenocorticism, death or euthanasia was treated as a competing risk, because these dogs could not have subsequently developed hypoadrenocorticism.

Cumulative incidences of hypoadrenocorticism by time after commencement of trilostane treatment were calculated using Stata's – stcompet – command. Ninety-five percent confidence intervals (CIs) were calculated using formula 4 described by Choudhury (2002). Cumulative incidences of hypoadrenocorticism (any permanency) were calculated accounting for death or euthanasia as a competing risk. Cumulative incidences of transient and permanent hypoadrenocorticism were also calculated, accounting for death or euthanasia and permanent or transient hypoadrenocorticism, respectively, as competing risks.

Seven potential risk factors for hypoadrenocorticism (any type) were assessed using univariable analyses. Competing risks regression was performed using Stata's – stcrreg – command. These analyses used the method of Fine and Gray (1999) and modelled the subhazard of hypoadrenocorticism calculated such that dogs that experienced the competing risk were no longer at risk of hypoadrenocorticism. Body weight, trilostane dose rate and frequency of administration could vary over time, so these were treated as time varying covariates.

Trilostane dose rate and/or dose frequency was reduced or discontinued in some dogs because the veterinary clinician was concerned that hypoadrenocorticism was developing. These dose rate reductions may have downwardly biased the estimated effect of dose rate on the risk of developing hypoadrenocorticism. A second approach was used to account for this bias; the data were modelled assuming for these dose rate reductions that the previous dose rate had instead been continued for 28 days after the actual date of reduction. Twenty-eight days was chosen, since it seemed likely that, had a dog been developing hypoadrenocorticism at the time of the dose rate reduction, it would have met our case definition within the next 28 days. Effects of dose frequency on risk of hypoadrenocorticism were also assessed in this way.

The competing risks regression models were unstable for analyses of anatomical localisation and neuter status because no dogs in the ADH group, and no unneutered dogs, developed hypoadrenocorticism. Thus, for these variables, incidence rates were calculated for each group as the number of dogs affected by hypoadrenocorticism divided by the sum of the number of days that each dog was at risk of developing hypoadrenocorticism, hereafter referred to as 'dog-days'. Incidence rates were compared using Stata's – iri – command. Exact binomial 95% CIs for the proportions of first occurrences of hypoadrenocorticism that were classified as each of transient and permanent were calculated using Stata's – cii – command.

Results

Numbers of dogs, outcomes and follow-up times

A total of 156 dogs were included in the study. Outcomes and times from commencement of trilostane treatment to outcomes for these dogs are summarised in Table 1. Hypoadrenocorticism was diagnosed in 24 dogs (15%). Hypoadrenocorticism could not be classified as transient or permanent in five dogs; two dogs died and one was euthanased due to hypoadrenocorticism. Two dogs were lost to follow-up. Of the remaining 19 dogs, 14 dogs (74%; 95% CI 49–91%) were categorised as having transient hypoadrenocorticism and five dogs (26%; 95% CI 9–51%) were classified as having permanent hypoadrenocorticism.

Clinicopathological findings at time of diagnosis of hypoadrenocorticism

Findings are summarised in Table 2; results were not available for some dogs. Electrolyte abnormalities were inconsistent, even in dogs diagnosed with permanent hypoadrenocorticism. The most consistent clinicopathological abnormality was azotaemia.

Incidences of hypoadrenocorticism

Cumulative incidences of hypoadrenocorticism by time from commencement of trilostane treatment are shown in Fig. 1. Cumulative incidence increased approximately linearly with time. Estimated incidence was 8% (95% CI 4–13%) at 320 days, 15% (95% CI 9–22%) at 754 days and 26% (95% CI 17–37%) at 1564 days after commencement of trilostane treatment. The cumulative incidence of transient hypoadrenocorticism was 10% (95% CI 5–17%) at 754 days and 17% (95% CI 9–28%) at 1564 days. The cumulative incidence of permanent hypoadrenocorticism was 4% (95% CI 1–9%) at 867 days and 6% (95% CI 2–13%) at 980 days.

[1] See: http://www.dechra-us.com/therapy-areas/companion-animal/endocrinology/canine-hyperadrenocorticism/products (accessed 25 October 2017).