Effect of phenobarbitone on the low-dose dexamethasone suppression test and the urinary corticoid: creatinine ratio in dogs

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Objectives To investigate potential effects of phenobarbitone on the low-dose dexamethasone suppression (LDDS) test and urinary corticoid to creatinine ratio in dogs in a controlled prospective study and in a clinical setting.

Animals Ten crossbreed experimental dogs and 10 client-owned dogs of mixed breeds treated chronically with phenobarbitone to control seizures.

Procedures Experimental dogs were allocated to treatment (6 mg/kg oral phenobarbitone, n = 6) and control (n = 4) groups. LDDS tests (dexamethasone 0.01 mg/kg intravenously, cortisol concentration determined at 0, 2, 4, 6 and 8 h) were conducted repeatedly over a 3-month period. Urinary corticoid to creatinine ratios were measured before LDDS tests. A single LDDS test was performed on 10 epileptic dogs.

Results LDDS and urinary corticoid to creatinine ratios in dogs were not affected by treatment with phenobarbitone.

Conclusions Phenobarbitone does not interfere with LDDS testing regardless of dosage or treatment time. Urinary corticoid to creatinine ratios are also unaffected.

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Key words: Dog, phenobarbitone, anticonvulsant, dexamethasone suppression test, urinary corticoid: creatinine ratio, human.

ACTH	Adrenocorticotrophic hormone	IV	Intravenous/ly
DST	Dexamethasone suppression test	LDDS	Low-dose dexamethasone suppression
HA	Hyperadrenocorticism	UCCR	Urinary corticoid: creatinine ratio

DSTs were developed in the 1960s and the single dose DST became the screening test for human HA.[1,2] It soon became apparent that dexamethasone failed to produce normal adrenocortical suppression in patients treated chronically with the anticonvulsants phenytoin and primidone.[3-5] Dexamethasone clearance was increased in human patients treated with phenytoin [6] and biliary excretion and hepatic conjugation of dexamethasone were enhanced in rats.[5] Increased clearance of dexamethasone due to hepatic enzyme induction was subsequently demonstrated with phenobarbitone therapy in humans.[7] It was concluded that failure of cortisol suppression in response to dexamethasone in humans on long-term anticonvulsants was due to increased hepatic metabolism of dexamethasone.[5,8]

This has led to concern about interpreting LDDS tests in dogs treated with anticonvulsants.[9,10] An uncontrolled study concluded that LDDS tests were unaffected by phenobarbitone administration although one of five dogs showed an abnormal result after 6 and 12 months of treatment despite normal endogenous ACTH concentrations and normal ACTH response tests.[11] It was not known whether this was due to phenobarbitone.

The UCCR test is based on the premise that corticoids measurable in a single, random, voided urine sample reflect the average blood corticoid concentration in the period during which the urine was formed. It readily distinguishes between healthy dogs and those with hyperadrenocorticism but it is also increased in stressed dogs with other diseases.[12,13] The test has also been considered unreliable in dogs with polyuria and polydipsia but it is not known whether this reflects the underlying disease process or the specific effects of polydipsia and polyuria.[12] The effect of phenobarbitone, a drug known to cause polyuria and polydipsia in some dogs, on UCCRs has not been reported.

Diagnosis of HA in dogs receiving phenobarbitone can be difficult. Phenobarbitone can produce clinical signs and laboratory findings mimicking those of HA, namely polyuria, polydipsia, lethargy, hepatomegaly and increased liver enzyme values.[11] As the LDDS test is generally regarded as the screening test of choice for canine HA the effect of phenobarbitone on the LDDS test in dogs requires investigation. UCCRs are simple, inexpensive screening tests for HA and if unaffected by phenobarbitone could be useful in dogs treated with phenobarbitone.

Materials and methods

Experimental study

Animals - Ten healthy crossbreed dogs, five entire males and five entire females, weighing 12.3 to 23.8 kg, were used in the experiment. They were housed individually in converted stables, walked once daily for 20 to 30 min, between 0600 h and 0900h and also allowed a 5 to 10 min run at feeding time. They were fed nutritionally complete, dry dog food (Eukanuba Premium, Iams) once daily, between 1600 h and 1800 h. Water was provided ad libitum.

All dogs were vaccinated, treated with anthelminthics (Drontal Allwormer,

Bayer) and acclimatised to housing, feeding and handling for 3 weeks prior to commencing the study. As trichuriasis was diagnosed during the study, anthelminthics (Drontal Allwormer, Bayer; Popantel Allwormer, Dover Laboratories) were administered monthly throughout. One dog required surgery for an intestinal foreign body during week 6 of the study thus phenobarbitone was not administered between day 4 of week 6 and day 2 of week 7 in this dog and sampling due on week 6 was postponed one week. Another dog sustained a fight wound during week 6 which necessitated surgery on week 6, after its LDDS test.

Dogs were distributed randomly into treatment (n = 6) and control (n = 4) groups. No phenobarbitone was administered during weeks 1 and 2. Phenobarbitone treatment commenced on day 1 of week 3 and continued for 12 weeks. The treated dogs were dosed with oral phenobarbitone at 6 mg/kg once daily at 0900 h. Phenobarbitone tablets (Phenobarbitone 30 mg, Sigma Pharmaceuticals) from a single batch were divided as necessary to give the closest approximation to 6 mg/kg. The range of calculated doses was 5.9 to 6.4 mg/kg but accuracy was limited by tablet divisions into quarters. Dosage adjustments because of weight changes were made after sampling trough phenobarbitone concentrations.

Samples and assays - Blood for serum phenobarbitone concentrations was collected at 0900 h on day 5 of weeks 1, 2, 4, 6, 8, 10, 12 and 14. Urine for measurement of UCCR was collected by free catch, catheterisation or cystocentesis between 0600 h on day 6 and 0900 h on day 7 of weeks 1, 2, 4, 6, 10 and 14. On day 7 of these weeks, blood was taken at 0900 h for plasma cortisol assay then dexamethasone sodium phosphate solution (Dexadreson, Intervet) was administered at 0.01 mg/kg IV. Blood samples for cortisol determination were then taken at 2 h intervals for 8 h. All blood was collected by jugular venipuncture.

Samples for measuring cortisol and phenobarbitone concentrations were collected into heparinised tubes and plain tubes respectively. Samples for cortisol were placed on ice then centrifuged and the supernatant was frozen immediately after separation. Urine was refrigerated for 24 h then 50 µL was mixed with 450 µL of distilled water and stored frozen for later creatinine measurement, the remainder being frozen for corticoid assays. Phenobarbitone assays were performed by a commercial laboratory (Macquarie Vetnostics). Cortisol assays were batched at the end of the study to avoid inter-assay variations for an individual dog's results.

Plasma cortisol and urinary corticoid concentrations were measured using a commercially available radioimmunoassay kit (Coat-A-Count, Cortisol Radioimmunoassay Kit, Diagnostic Products) according to the manufacturer's directions. The assay sensitivity, estimated as the lowest cortisol concentration required to displace 10% of bound tracer, was 5.4 nmol/L. Specificity was demonstrated by parallel competitive binding curves for serial dilutions of pooled dog plasma and human standards. The intra- and inter-assay coefficients of variation were 7.7 and 10.5% respectively.

Statistics - Serum phenobarbitone concentrations and UCCR results were each subjected to a one - way analysis of variance with repeated measures design. Plasma cortisol concentrations during LDDS tests were analysed using a multiple analysis of variance with repeated measures design. Statistical significance was accepted at the 5% level.

Clinical study

Ten dogs (numbered 1 to 10) of various breeds aged between 1.5 and 9 years, receiving phenobarbitone for epilepsy, were recalled for the study. The dogs had been treated with oral phenobarbitone for 14 to 92 months at doses of 3.9 to 14.4 mg/kg/d (mean 8.6, SD 3.6, median 7.9). The daily dose was divided and administered twice or thrice daily. Four dogs (1, 2, 3 and 10) were also receiving potassium bromide (Epibrom, Equisci International), which is not reported to induce or inhibit hepatic drug metabolising enzymes or to compete for protein binding sites with other anticonvulsants.[14]

The dogs were fasted from 2000 h until testing the following morning at 0830 h. All dogs were examined thoroughly and weighed before having blood taken at 0900 h for measurement of serum phenobarbitone and basal plasma cortisol concentrations. The dogs were then given 0.01 mg/kg dexamethasone sodium phosphate IV and their morning dose of phenobarbitone. Blood for cortisol assays was taken 4 and 8 h later. Sample handling, phenobarbitone measurements and cortisol assays were done as previously.

Results

Experimental study

Serum phenobarbitone concentrations in treated dogs did not change over time. The means for weeks 6, 8, 10 and

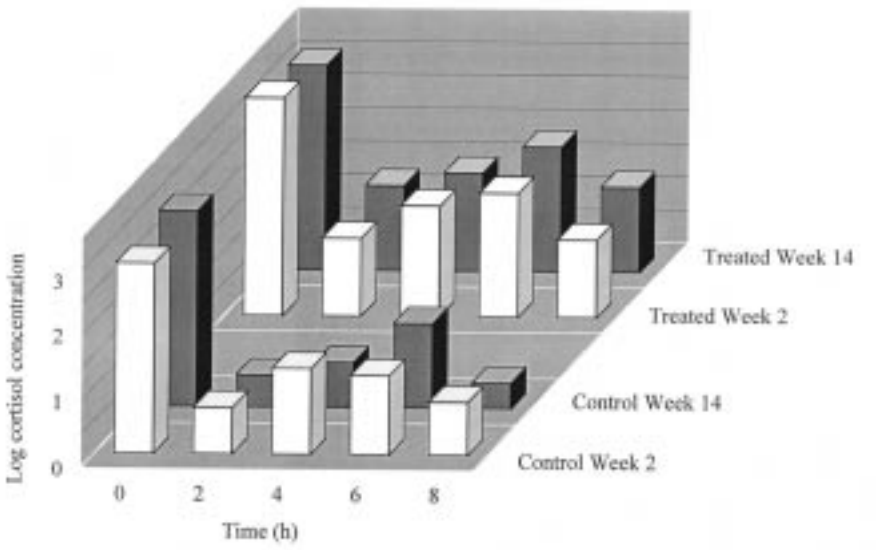

Figure 1. Log mean cortisol (nmol/L) at 0, 2, 4, 6 and 8 h after dexamethasone (0.01 mg/kg IV) for control dogs and treated dogs at weeks 2 and 14.

14 were lower than the laboratory's suggested therapeutic range of 65 to 194 µmol/L.[15] There was a significant decrease in UCCR between weeks 1 and 2, before phenobarbitone treatment commenced. After week 1, all UCCRs except one were below the reference limit (20×10^{-6}). The one abnormal UCCR noted at week 6 (22×10^{-6}) was attributed to stress due to a fight wound in that dog.

Plasma cortisol concentrations during LDDS tests showed no differences over time except between weeks 1 and 2, that is, before phenobarbitone treatment commenced. LDDS results were all normal when assessed on absolute values. However, suppression was difficult to assess in some dogs, as baseline cortisol concentrations were very low, often below the threshold considered consistent with suppression. If suppression of baseline cortisol concentration by 50% or more was used as the criterion, then some LDDS results for treated and control dogs would be considered abnormal. Baseline cortisol concentrations for these tests range from 0.5 nmol/L to 22 nmol/L, all except one below the 20 nmol/L normally observed after suppression. However, there was no significant difference between treated and untreated groups and no change over time in phenobarbitone-treated dogs (Figure 1).

In these dogs, 36 of 60 baseline cortisol concentrations were less than or equal to the lowest end of our reference range (25 to 75 nmol/L). Some dogs had concentrations that would more commonly be noted with hypoadrenocorticism. One dog had baseline cortisol concentrations of 5, 10, 1 and 5 nmol/L at weeks 4, 7, 10 and 14 respectively but was active, healthy and had normal responses to ACTH in subsequent studies.[16]

Clinical study

The phenobarbitone doses, serum concentrations, duration of therapy and LDDS results for each dog are listed in Table 1. Mean serum phenobarbitone concentration was 110 µmol/L (range 72 to 171 µmol/L). All concentrations were in the suggested therapeutic range of 65 to 194 µmol/L. Results of LDDS tests in 9 of 10 dogs were consistent with normal adrenal function; one dog (dog 6) showed inadequate suppression.

Table 1. LDDS test results and phenobarbitone dose, serum concentration, and treatment duration for 10 epileptic dogs.

Dog	Phenobarbitone dose mg/kg	Serum phenobarbitone µmol/L	Treatment time months	Cortisol nmol/L		
				0 h	4 h	8 h
1	9.3	135	92	31	0	2
2	7.9	86	65	70	4	4
3	14.4	171	35	52	4	3
4	3.9	102	15	205	17	10
5	5.0	101	15	190	13	9
6	10.2	99	50	72	25	56
7	6.0	72	16	53	6	6
8	9.4	89	18	71	10	7
9	13.8	119	32	112	8	13
10	5.6	127	14	70	8	3

Discussion

Phenobarbitone did not affect LDDS testing in experimental dogs in this study. The decrease in cortisol concentrations between weeks 1 and 2 in the pre-treatment period were attributed to the dogs becoming more accustomed to blood sampling. UCCR results decreased similarly between weeks 1 and 2 and phenobarbitone had no effect.

The effect of stress and excitement on plasma cortisol concentrations in dogs should not be underestimated. Resting cortisol concentrations became very low in many of the experimental dogs and, given the assay sensitivity, the LDDS responses were occasionally difficult to assess. This would not affect clinical interpretation but hindered assessment of effects of phenobarbitone on individual results. Many baseline cortisol concentrations were as low as those seen in dogs with hypoadrenocorticism. These dogs had bonded with the first author and, in essence, were being handled and sampled by their owner in their home environment. Our reference range for baseline cortisol concentrations was established on dogs brought into the hospital by clients and may reflect the additional stress and excitement involved. Low baseline cortisol concentrations (21 to 34 nmol/L) have been noted previously in well-conditioned dogs.[17]

The one abnormal LDDS result in the epileptic dog 6 may reflect the test's specificity. Specificity was greater than 0.95 in one study[13] but only 0.73 in another.[18] False positives in normal dogs may reflect variation in dexamethasone metabolism and clearance.[9] In dogs with non-adrenal illness, specificity is much lower with 38% and 56% of dogs failing to demonstrate cortisol suppression at 4 and 8 h respectively. [13] Dog 6 had no clinical or biochemical findings suggesting HA but was very nervous, as were most of the clinical patients studied. Unlike the other dogs, this dog defaecated voluminously and frequently (six times over 24 h), possibly indicating gastrointestinal disease (one of the disease categories in the study of Kaplan);[13] dietary modification has since led to resolution of this problem.

It is possible that the abnormal LDDS in dog 6 was caused by phenobarbitone. Dexamethasone at 0.01 mg/kg suppresses plasma cortisol for at least 16 h in normal dogs.[19] Plasma dexamethasone concentrations vary greatly in healthy dogs after 0.01 mg/kg and 0.1 mg/kg IV.[9] Whether this variability affects the response of the hypothalamic-pituitary axis to dexamethasone is unknown.[9] If plasma dexamethasone concentration was lower in dog 6 than in the other dogs, increased dexamethasone metabolism induced by phenobarbitone could have lead to inadequate cortisol suppression.

Phenobarbitone increases the rate of dexamethasone metabolism in humans, altering DST results. The normal LDDS results in 15 of 16 dogs in this study suggest that a comparable effect in dogs does not occur or is insufficient to influence the LDDS test. The standard human DST procedure is to administer 1 mg dexamethasone orally at 2300 h,

when endogenous cortisol secretion is normally low and to collect samples for serum cortisol assays the next day at 0800 h and sometimes at later periods such as 1600 h and 2300 h. [1,20] The elimination half-life of intravenous dexamethasone in humans is similar to that in dogs.[21,22] The 1 mg dose of dexamethasone is 0.01 to 0.02 mg/kg for body-weights of 50 to 100 kg, comparable to the standard canine dose of 0.01 mg/kg. Dexamethasone metabolism in humans is sufficiently increased by phenobarbitone to affect results of the 9h sample. The effect of phenobarbitone at 4 h is unknown.

Two factors that differ between the DST in humans and the LDDS test in dogs are the route of administration and the lack of circadian rhythm for corticosteroid secretion in dogs.[23,24] The route of administration may be a critical difference. Plasma concentration following a single oral dose of dexamethasone, as used in humans, is dependent on volume of distribution and rate and extent of drug absorption (bioavailability) as well as drug clearance.[21] The reported bioavailability of dexamethasone in normal humans is approximately 80%[25] but, due to presystemic clearance (first-pass effect), it may be only 10 to 25% in some patients.[26] Interestingly, all patients with dexamethasone bioavailability below 50% were receiving phenytoin whereas two of three patients with good bioavailability were not. As phenytoin did not impair gastrointestinal absorption of dexamethasone in rats,[5] possible effects of the oral route of dexamethasone administration on the human DST have not been examined.

Hypothalamic-pituitary-adrenal axis suppression correlates with plasma dexamethasone concentration and is thus influenced by pharmacokinetic variations.[27] Although dexamethasone metabolism is increased by anticonvulsants, reduced bioavailability because of an enhanced first-pass effect may be the main cause of problems with the DST in humans. Further studies into the effects of phenobarbitone on dexamethasone pharmacokinetics in humans, including trials with oral and IV DSTs, would be necessary to investigate this.

It was interesting that the mean serum phenobarbitone concentrations in the six experimental dogs failed to reach suggested therapeutic concentrations in 4 of the 6 weeks tested; the maximum phenobarbitone concentration was 96 µmol/L. All 10 clinical cases, however, had serum phenobarbitone concentrations within the therapeutic range; four of these dogs were receiving daily doses of phenobarbitone equal to or less than that of the experimental dogs and had serum phenobarbitone concentrations of 72 to 127 µmol/L.

The discrepancy was surprising as, although there is a poor correlation between dose and serum concentrations,[28,29] one would assume that with longer treatment duration, phenobarbitone tachyphylaxis would necessitate increasing phenobarbitone doses to maintain therapeutic serum concentrations.[30,31] Frey[30] reported lengthened phenobarbitone half-lives in some individual dogs and it is possible this could have occurred in the clinical cases. A more likely explanation is that dividing the dose eliminates the effect of a shortened half-life and enables therapeutic concentrations to be maintained.

Routine clinical recommendations have been to divide the phenobarbitone dose, despite pharmacokinetic studies that suggest once daily dosing should be sufficient.[31,32] The findings in this study provide some support for the current recommendations that divided dosing is more likely to produce therapeutic concentrations of phenobarbitone. Pharmacokinetic studies examining the effects of dose frequency on serum phenobarbitone concentrations would be required to investigate this further.

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Effects of phenobarbitone on serum biochemical tests in dogs

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Objectives To investigate effects of phenobarbitone on serum activities of alanine aminotransferase, alkaline phosphatase and gamma-glutamyl transferase and concentrations of bilirubin, albumin, cholesterol and total protein in dogs.

Animals Ten crossbreed experimental dogs and 10 client-owned dogs of mixed breeds treated chronically with phenobarbitone to control seizures.

Procedures Experimental dogs were allocated to treatment (6 mg/kg oral phenobarbitone, n = 6) and control (no treatment, n = 4) groups in which serum biochemical tests were performed at intervals during a 3-month period. Biochemical tests were performed once on the 10 epileptic dogs.

Results Phenobarbitone caused increased serum alkaline phosphatase activity but did not affect gamma-glutamyl transferase activity or bilirubin, cholesterol, albumin and total protein concentrations. Phenobarbitone had minimal effect on alanine aminotransferase activity.

Conclusions Individual dogs treated with phenobarbitone may have small increases in serum alanine aminotransferase activity and variable increases in alkaline phosphatase activity but are unlikely to have alterations in gamma-glutamyl transferase activity or bilirubin, cholesterol, albumin or total protein concentrations.

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Key words: Dog, phenobarbitone, alanine aminotransferase, alkaline phosphatase, gamma-glutamyl transferase, hypertriglyceridaemia.

ALP	Alkaline phosphatase	GGT	Gamma-glutamyl transferase
ALT	Alanine aminotransferase	TP	Total protein

Phenobarbitone and primidone are the most effective drugs for long term anticonvulsant therapy in dogs.[1,2] As there is a greater potential for behavioural side-effects and hepatotoxicity with primidone, phenobarbitone is widely regarded as the drug of choice for chronic therapy.[1,2] However, phenobarbitone has also been reported to cause hepatotoxicosis in dogs.[3]

Anticonvulsants may affect results of laboratory tests commonly used to assess hepatic abnormalities. Increased serum activities of ALT, ALP and GGT have been reported and these changes have been attributed to drug-induced enzyme synthesis and low-grade hepatocellular injury, with larger increases possibly associated with morphologic evidence of liver injury.[4,5] Most of the information about effects of anticonvulsants on the liver has been based on data for primidone and anticonvulsant combinations[6-8] or on studies with few dogs receiving large doses of phenobarbitone.[9-11] Evidence exists for phenobarbitone-induced increases in ALP activity [10-13] but effects of phenobarbitone on ALT have, until recently,[11] been based on a study using only two dogs [9] and effects on GGT have not been investigated.

Materials and methods

Animals

Dogs from a study of the effects of phenobarbitone on adrenocortical function tests[14] were used in this study. There were 10 experimental dogs (6 dosed with phenobarbitone, 4 controls) and 10 client-owned epileptic dogs (numbered 1 to 10) receiving phenobarbitone to prevent seizures.