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Inefficacy of selegiline in treatment of canine pituitary-dependent hyperadrenocorticism

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Objective To evaluate selegiline, a monoamine oxidase-B inhibitor, for treating dogs with pituitary-dependent hyperadrenocorticism.

Design Prospective clinical trial using client-owned dogs with pituitary-dependent hyperadrenocorticism treated at The University Veterinary Centre, Sydney, from September 1999 to July 2001.

Procedure Eleven dogs with pituitary-dependent hyperadrenocorticism treated with selegiline were monitored at days 10, 30 and 90 by clinical examination, tetracosactrin stimulation testing, urinary corticoid:creatinine ratio measurement and client questionnaire. Endogenous adrenocorticotropic hormone measurements were also performed on most dogs on days 0 and 90.

Results No dog treated with selegiline had satisfactory control of disease.

Conclusion Selegiline administration was safe and free of side-effects at the doses used, but did not satisfactorily control disease in pituitary-dependent hyperadrenocorticism affected dogs.
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ACTH	Adrenocorticotropic hormone
ANOVA	Analysis of variance
CNS	Central nervous system
CRH	Corticotropin releasing hormone
CT	Computed tomography
LDDST	Low-dose dexamethasone suppression test(s)
MOA	Monoamine oxidase
MOA-A	Monoamine oxidase-A
MOA-B	Monoamine oxidase-B
PDH	Pituitary-dependent hyperadrenocorticism
SEM	Standard error of mean
UCCR	Urinary corticoid:creatinine ratio
UVCS	University Veterinary Centre, Sydney

Pituitary-dependent hyperadrenocorticism is one of the most commonly recognised endocrine diseases of mature dogs. Medical treatment with mitotane or ketoconazole can be unsatisfactory because of drug side-effects or lack of efficacy and selegiline has been suggested as an alternative.[1,2] Selegiline ((R)-(-)-N, 2-propynylphenethylamine hydrochloride or l-deprenyl) is a selective, irreversible inhibitor of MOA-B and acts centrally to increase dopamine concentrations.[2] Its main use is to treat Parkinson's disease in people.[3] It has been reported as useful to treat canine geriatric cognitive dysfunction.[4] Recent interest has focussed on its potential for treating excessive ACTH secretion in PDH-affected dogs, based on the belief that dopamine secretion from higher centres regulates ACTH secretion from the pituitary gland.[1]

As in other species, the canine pituitary gland has distinctly separate anatomical and functional areas. The pars intermedia is separated from the rest of the adenohypophysis by Rathke's cleft. The primary secretory products of the pars intermedia in the dog are α-melanocyte-stimulating hormone from 'A' cells (melanotrophs) and small amounts of ACTH from 'B' cells (corticotrophs).[5] These A and B cells are believed to be under the same regulatory controls and respond similarly in vitro to stimulation by CRH and inhibition by dopamine and somatostatin.[6,7] This is not so clearly the case in vivo, perhaps because the pars intermedia, having scant vascularisation, is not greatly influenced by blood-borne products from the hypothalamus.[6,8] Instead, it is innervated and controlled

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mainly by secretory products, primarily dopamine, from nerve fibres originating in the hypothalamus.

Corticotrophic cells in the pars distalis resemble B cells of the intermediate lobe, but their secretory activity is regulated by blood-borne substances, especially CRH, of the hypothalamus.[9] The hypothalamus and higher centres that control the pars distalis are themselves influenced by various endocrine and non-endocrine factors.[8] The adenohypophysis is also influenced by negative feedback effects of the secretory products of its target organs, both directly and via higher centres.[8]

Investigators have attempted to identify mechanisms controlling pituitary secretion of ACTH in the dog and, in particular, to determine the effect of dopamine (or its absence) on secretory activity of corticotrophs of the pars intermedia and pars distalis.[6-8,10-14] Some data are inconclusive or provide conflicting results but the evidence suggests that endocrine and neuroendocrine substances from higher centres affect corticotroph cells of the pars distalis and the pars intermedia differently. Dopamine appears to have a greater effect on suppressing ACTH production by the pars intermedia. The nature of this influence is an important but unresolved issue when considering the rationale for selegiline treatment for canine PDH, because only 30% or less of pituitary tumours in dogs with PDH appear to arise in the pars intermedia.[15]

In addition to questions as to the effect of dopamine on ACTH secretion, there are doubts as to the effect of selegiline on dopamine concentrations in the CNS and pituitary gland. Selegiline has been shown to decrease MOA-B activity in the canine brain, with no effect on MOA-A or concentrations of dopamine, serotonin or metabolites of these substances.[16] MOA inactivates and metabolises dopamine in the CNS, but species differ in the predominant form of MOA present, and there is disagreement as to the predominant form of MOA in the canine brain. One report[16] concluded that dopamine must be metabolised by MOA-A rather than MOA-B in the canine brain, which would imply that selegiline would be of no use in altering dopamine concentrations. However metabolites of selegiline, in particular phenylethylamine, which facilitates catecholaminergic transmission, might influence the effect of dopamine in the CNS, if not the concentration.[16]

On balance, the evidence for a major role of dopamine (or selegiline) in influencing ACTH secretion in normal dogs is not strong, but interspecies anatomical and functional differences of the pituitary gland hinder interpretation. Additional differences may exist in abnormal pituitary tissue, for example altered receptors or post-receptor processing. Furthermore, all parts of the pituitary are influenced by interactions with the other parts, and none can be considered to act in isolation of these influences.[17] Findings in vitro using pituitary extracts or homogenised pituitary samples do not always correlate with in vivo results, where the interaction and complexity of multiple endocrine and neurological influences are at play. The inability to sample hormone and neurotransmitter concentrations in portal blood supplying the pars distalis also severely restricts clarification of in vivo activity of potentially important endocrine regulators.

The value of dopamine agonists for treatment of PDH would therefore need to be demonstrated by controlled clinical trials for such drugs to have convincing claims to efficacy in this disease. So far, there have been two published clinical studies examining the effects of selegiline in dogs with PDH.

The first consisted of a pilot study in seven dogs,[18] then other dogs were enrolled and more detailed accounts followed.[1,2,19] In total, 90 client-owned dogs with PDH were given selegiline at 1 mg/kg (52 dogs) or 2 mg/kg (38 dogs) every 24 h. Response to treatment was assessed subjectively by the owner and on physical examination by a veterinarian. Haematological examinations, biochemical tests and LDDST were performed monthly. Of 52 dogs studied for 6 months, eight (15%) were classified as having normalisation of their LDDST and reduced mean plasma cortisol concentrations. Normalisation of the LDDST was defined as LDDST results within the reference range (not stated) at one or more points in time,[2] implying that a normal LDDST on any one of six occasions constituted successful treatment. All clinical variables were reportedly improved at every time point, usually to a significant degree. An unstated proportion of patients improved in only one or two variables. However improvement does not necessarily prove resolution of a problem and some improvements (mental alertness, activity levels) could be attributable to the central stimulatory effects of metabolites of selegiline – specifically amphetamine and phenylethylamine. These reservations aside, these experienced and specialist clinical investigators concluded that selegiline had merit in treating canine PDH. No noteworthy adverse drug effects were noted during the trial.

In a related study,[20] geriatric Beagle dogs, not affected by PDH, treated with 1 mg/kg selegiline once daily for 1 year had significantly lower plasma cortisol concentrations in response to CRH stimulation testing than did untreated dogs. However, ACTH concentrations after CRH stimulation did not differ between groups, making it difficult to attribute reduced cortisol concentrations to a selegiline effect on pituitary ACTH secretion.

The second study of selegiline use in PDH-affected dogs[21] reached different conclusions: ten dogs were monitored with a similar protocol as previously but also had monthly UCCR determination, abdominal ultrasound examination and CRH response testing, as well as ACTH stimulation tests and CT scans before and after 6 months of treatment. Unlike the earlier study, all subjective assessments were made by one individual. Of the ten dogs, eight remained in the trial for the full 6 months. The response to treatment was extremely variable and clinical improvements were inconsistent. Improvement in activity levels and lethargy were noted and polyphagia reduced. Although 70% of owners thought water intake was lowered, only 30% had decreased intake when measured. The size of the adrenal glands increased more than 20% in four dogs over the 6 months and did not decrease in any dog. Pituitary masses, assessed by CT, increased in size in four of the seven dogs with visible masses. UCCR, and CRH and ACTH stimulation tests were unchanged in all dogs, but four had normal LDDST findings after 6 months and mean baseline ACTH concentrations were lower. The conclusion was that selegiline could not be recommended for treatment of PDH in dogs because of lack of consistent improvement in clinical signs and endocrine abnormalities.

The conflicting findings of previous studies prompted this clinical trial to evaluate the suitability of selegiline as an alternative therapy for the management of PDH in the dog.

Materials and methods

Eleven dogs with naturally occurring and previously untreated PDH were selected from patients presented at the UVCS between October 1999 and July 2000. Dogs selected for inclusion had no evident concurrent systemic disease, and owners agreed to participate in the trial.

The diagnosis of PDH was based on appropriate historical and/or physical findings,[22] supported by LDDST results as detailed below. All dogs underwent abdominal ultrasound examination to exclude adrenal neoplasia and to screen for clinically silent intra-abdominal conditions. Ultrasonographic changes compatible with steroid hepatopathy and/or bilaterally symmetrical enlargement of adrenal glands (∅ 15 mm wide at either pole of either gland) were considered consistent with PDH, but their absence did not prevent inclusion.

As an additional test to confirm pituitary-dependent disease, endogenous plasma ACTH concentration was measured in ten of the dogs prior to starting treatment. An endogenous ACTH concentration > 45 ng/L was considered consistent with PDH. Endogenous ACTH was also measured at completion of the trial in seven of the ten that completed the trial period. Adrenal response to tetracosactrin was tested in all dogs prior to selegiline treatment.

Table 1. Reference ranges.

Tetracosactrin response test

Untreated hyperadrenocorticoid patient:

Baseline cortisol....	25 - 75 nmol/L.....normal baseline
1-h cortisol.....	200 - 400 nmol/L .....normal response
1-h cortisol.....	400 - 600 nmol/L.....hypersecretion, suspicious of hyperadrenocorticism
1-h cortisol.....	> 600 nmol/L.....supportive of hyperadrenocorticism

Treated hyperadrenocorticoid patient:

Baseline cortisol.....	25 - 75 nmol/L.....normal baseline
Baseline and 1-h cortisol	≤ 25 nmol/L ..... excessive control of hyperadrenocorticism
1-h cortisol.....	25 - 75 nmol/L..... 'tight' control of hyperadrenocorticism
1-h cortisol.....	75 - 125 nmol/L..... 'acceptable' control of hyperadrenocorticism

Low dose dexamethasone suppression test

Baseline cortisol.....	25 - 75 nmol/L.....normal baseline
4-h cortisol.....	≤ 20 nmol/L..... normal suppression
8-h cortisol.....	≤ 20 nmol/L.....normal suppression

Urinary corticoid:creatinine ratio

$\leq 15 \times 10^{-6}$ .....normal dog or 'tight' control of hyperadrenocorticism

$\leq 25 \times 10^{-6}$ ..... 'acceptable' control of hyperadrenocorticism

Selegiline was given orally at 2 mg/kg once daily for 3 months. The medication was available as 30 mg, 10 mg and 2 mg tablets (Anipryl®, Mikart Inc, Atlanta, Georgia) or 5 mg tablets (Selgene®, Alphapharm, Carole Park, Australia). Anipryl tablets could not be readily halved because the tablets were octagonal, so dosages were rounded to 1.5 to 2.0 mg/kg/day, and if this dose was tolerated well it was rounded up to the nearest dose at the first recheck.

Owners were asked to return dogs on days 10, 30 and 90 of treatment and to record the 24 h water intake prior to each visit. They were also asked to provide a morning urine sample from the dog each time for UCCR determination, but not all owners were able to do this. At each visit, owners completed a questionnaire about the dog's general health, thirst, appetite, activity, panting and abnormal events such as vomiting or behavioural changes. The first author (JB) examined all dogs, assessed medication usage, and performed a tetracosactrin response test, usually between 10 am and 1 pm. The physical examination findings were assessed subjectively, and recorded on the standard UVCS clinical examination form.

At 90 days the efficacy of selegiline in relieving clinical signs and resolving endocrine dysfunction, as reflected by the tetracosactrin stimulation, was evaluated: either continuation of selegiline or a change to mitotane administration was recommended based on this assessment, but the decision was left to the owner. Neither choice offered a financial advantage for the owner because all treatment costs were subsidised for the subsequent 3 months of treatment regardless of whether selegiline or mitotane was selected.

Test protocols and sample collection

LDDST — A 0-h blood sample was collected for plasma cortisol determination and the dogs were injected with 0.01 mg/kg dexamethasone via the cephalic vein. Blood samples were collected at 4 h and 8 h afterwards for cortisol measurement. Dogs were considered to have failure of normal pituitary-adrenal axis function if plasma cortisol concentration was not suppressed appropriately, as outlined in Table 1. Suppression of cortisol concentrations at 4 h (to less than 50% of baseline values or less than 20 nmol/L) with escape by 8 h was considered supportive of a diagnosis of PDH.

Tetracosactrin stimulation test — A 0-h blood sample was collected for plasma cortisol determination and then 5 µg/kg tetracosactrin (also known as cosyntropin, a synthetic ACTH analogue) was injected via the cephalic vein. The post-tetracosactrin venous blood sample was collected at 1 h for cortisol measurement.[23] Interpretation of findings was as shown in Table 1.

Endocrine assays — Plasma cortisol and urinary corticoid assays were performed using a commercial radioimmunoassay kit (Coat-A-Count®, Cortisol Radioimmunoassay Kit, Diagnostic Products, Los Angeles, USA), previously validated for measurement of canine cortisol.[24] Urine immunoreactive cortisol (urine 'corticoid') was measured using the same commercial radioimmunoassay kit, which has been used previously to measure urine corticoids in dogs.[25] Blood samples (3 to 5 mL) were collected by jugular venipuncture. The heparinised samples were centrifuged and the supernatant frozen at -20°C within 10 min of collection. Urine samples were stored at -20°C. Batched samples were assayed for cortisol at the end of every week. Urine creatinine concentration was determined using 50 µL diluted 1:10 with 450 µL distilled water and processed by a Cobas Mira discrete biochemical analyser (Hoffmann-La Roche, Basel, Switzerland) with creatinine reagents from Trace Scientific, Noble Park, Australia. The UCCR was calculated by dividing urine cortisol concentration (nmol/L) by urine creatinine concentration (nmol/L). For endogenous ACTH measurement, 5 mL blood collected by jugular venipuncture into sodium-EDTA was centrifuged immediately for 5 min and separated plasma was

stored at -20°C. Batched samples were assayed at the end of each month for ACTH using a commercial radioimmunoassay kit (RSL ^{125}I ACTH, ICN Biomedical Inc, Costa Mesa, USA), previously validated for dogs.[26]

Statistical analysis — Data were analysed using Statistix Ver 7, Analytical Software, Tallahassee, USA. A Shapiro-Wilk W Test was conducted for normality. As data were not normally distributed, non-parametric analyses were appropriate. A Kruskall-Wallis one way analysis of variance was used to detect overall differences in measured values between days 0, 10, 30, 90, +/-180 and final measurements. Mean ranks were compared to determine the point at which the differences occurred, that is, detecting between-day effects. The Kruskall-Wallis test could not be used for the selegiline group ACTH data as there were too many ties, therefore the parametric ANOVA was used.

Results

Owner compliance with treatment recommendations, determined on the basis of questioning and assessing amounts of medication used between visits, was considered excellent in dogs completing the trial.

The mean and median ages of dogs were 11 years (range 7 to 14). There were two entire and three castrated males and six spayed females. The mean body weight was 11.7 kg (range 3 to 22).

One dog had an episode of acute pancreatitis at day 60, but recovered after treatment in hospital for 1 week. Selegiline administration was resumed after a 7 day break and the dog completed a total of 90 days treatment.

One dog was euthanased prior to completing the study. It suffered acute shoulder luxation at day 75, requiring surgical stablisation, but the owner requested the dog be euthanased because of its poor condition and profound muscle weakness. Treatment results for this dog were included in this report, but 90-day data were unavailable. The other ten dogs completed 90 days of selegiline administration.

Case recruitment to the trial ceased with the 11th dog because the drug appeared to be ineffective (as described later), and because only 6/11 of the enrolled dogs remained alive 3 months after completing the 90 day treatment.

Of the four dogs that were euthanased or died after completing the trial, one was euthanased at 2 weeks because the owner was unhappy about the dog's quality of life and was unwilling to continue medical treatment for PDH. Another was treated successfully for 1 month with mitotane then euthanased because of acute intervertebral disc prolapse and pelvic limb paralysis. The third dog was also treated with mitotane for 1 month, but then died after suffering acute respiratory distress that was thought attributable to pulmonary thromboembolism. A fourth dog was stabilised successfully on mitotane treatment for 3 months but then euthanased because of inflammatory lung disease and congestive heart failure.

At no time did any dog in the selegiline group have an ACTH response test that indicated control of PDH. The endocrine test results are depicted in Figure 1.

Mean basal cortisol concentration at day 0 was 170 nmol/L (median 158, range 57 to 299). There was no discernible trend in these values over time: day 10 mean was 181 nmol/L (median 163, range 104 to 332); day 30 mean was 156 nmol/L (median 145, range 47 to 282); day 90 mean was 186 nmol/L (median

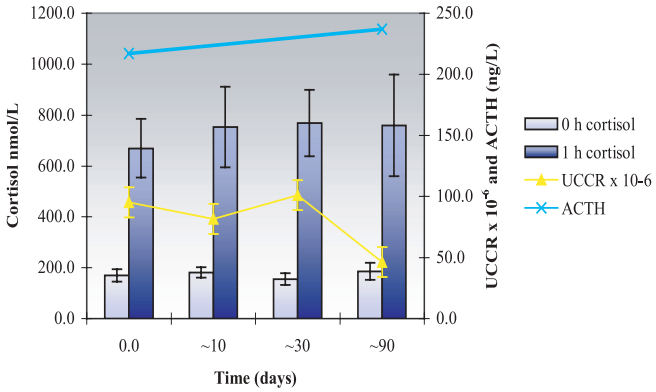

Figure 1. Endocrine test results: plasma cortisol concentrations before (0-h) and after (1-h) tetracosactrin administration, urine corticoid:creatinine ratios (UCCR), and endogenous ACTH concentration in 11 dogs with pituitary-dependent hyperadrenocorticism before and during treatment with selegiline. Data shown as means; bars indicate SEM.

155, range 37 to 355). Mean cortisol concentration 1-hour post-ACTH also showed no apparent trends. The 1-hour cortisols at day 0 were mean 669 nmol/L (median 582, range 164 to 1380); day 10 mean was 753 nmol/L (median 556, range 307 to 2014); day 30 mean was 769 nmol/L (median 630, range 326 to 1728); day 90 mean was 759 nmol/L (median 476, range 432 to 2543). There was no significant difference in the group mean baseline or 1-hour cortisol concentration over time (P = 0.83 and P = 0.89 for baseline and 1-hour values, respectively).

The ACTH concentrations did not change with time (Figure 1), either as a trend in any individual animal, or as a group mean (P = 0.80). Group mean endogenous ACTH concentration at day 0 was 217 ng/L (median 160, range 67 to 500, SEM 45). At day 90 the group mean ACTH was 237 ng/L (median 168, range 72 to 500, SEM 69).

The pre-treatment UCCR mean was 95.2 x 10^{-6} (median 22.7, range 1.1 to 415.0). There appeared to be an overall downward trend in this measurement: day 10 UCCR mean was 81.6 x 10^{-6} (median 15.0, range 7.1 to 542.0); day 30 UCCR mean was 101.0 x 10^{-6} (median 24.5, range 4.1 to 375); day 90 UCCR mean was 46.3 x 10^{-6} (median 20.5, range 8.2 to 163.0). This downward trend coincided with the loss of an animal on day 75 that had consistently given the highest (and outlying) UCCR for the group. If this animal was excluded from calculation of UCCR means at all test times, then mean UCCRs were 55.2 on day 0 and 24.1, 61.9, 46.3 for days 10, 30 and 90 respectively. There was, however, no statistically significant change in the mean UCCRs when calculated with and without the outlier (P = 0.81 or P = 0.65, respectively).

With regard to the owners' questionnaire, owners reported 'overall improvement' initially in seven of the eleven dogs (64%), but by the third recheck at 90 days, only five of the remaining ten dogs (50%) were reported to have 'overall improvement', one was considered to have deteriorated and four were unchanged compared to before treatment. All owners were unreliable in objectively measuring 24-hour water intakes, because of multiple animals or non-compliant people in the house, or added inconvenience. Subjectively, three of the eleven animals were thought by the owners to be drinking less than before treatment, at all time points, but in only one of these was this associated with observ-

ably less urination. Activity levels were considered increased in five of eleven dogs (45%) and general demeanour to be improved in four (36%). Appetite was unchanged in all but one dog, where it may have been increased at day 90. A single dog was reported to be panting less than before selegiline treatment and to be sleeping less during the day. Interestingly, this was also one of the dogs thought to be drinking and urinating less and improved overall. Time spent sleeping increased in one dog.

Abnormalities observed by owners during treatment were occasional vomiting or diarrhoea in one dog, occasional diarrhoea in another, and occasional ptyalism in a third. These signs did not persist or require intervention or withdrawal of the drug.

No dog was found to have improved with respect to physical findings on veterinary clinical examination.

As none of the ten dogs that completed the 90 day trial had convincing evidence of control of PDH, drug administration was gradually withdrawn in all dogs over a period of 2 to 4 weeks, and they were then treated with mitotane. One dog was euthanased before satisfactory control of disease could be achieved on mitotane. All others stabilised satisfactorily on mitotane, on the basis of clinical response and baseline and 1-hour post ACTH cortisol concentrations of ≤ 125 nmol/L. Two subsequently became iatrogenically hypoadrenocorticoid and were treated with cortisone (both dogs) and fludrocortisone (one dog).

After 3 months on mitotane, one owner decided to cease administering it due to difficult financial circumstances. This client preferred selegiline treatment because of the lower cost of maintenance after the subsidised trial finished, since no further endocrine testing was recommended, and because the dog had seemed particularly active and well on selegiline. This was the dog that had reduced panting, sleeping, reduced water consumption and urination. This dog appears to have static disease, based on clinical signs, but no further endocrine testing was performed.

Discussion

Although owners of several dogs reported subjectively an overall improvement in their dog's condition while given selegiline, no treated dog had ACTH stimulation test results that indicated improved or controlled endocrine status during the 90-day trial. In addition, UCCR values did not improve with treatment.

Endogenous ACTH concentrations did not decrease significantly over the 90-day period in dogs in which it was measured. Given the proposed mechanism of action of selegiline in acting centrally to decrease pituitary ACTH secretion, this is not what would be expected if the drug were effective. It is, however, in keeping with the lack of clinical or endocrine improvement. A previous article reported a significant decrease in endogenous ACTH (but normalisation in only 1/10 dogs), without other convincing evidence that endocrine function had improved.[21]

It has been argued[2] that tetracosactrin or ACTH response testing is not an appropriate measure of response to selegiline, because the drug is used in PDH to 'normalise' pituitary function rather than to limit the adrenals' ability to respond to pituitary ACTH hypersecretion. However it is logical to expect that if selegiline restores normal pituitary function and its sensitivity to feedback inhibition and hypothalamic control, the adrenal glands should return to normal size and secretory activity, and cease to respond in an exaggerated fashion to tetracosactrin stimulation. While response to ACTH indicative of iatrogenic hypoadrenocorticism, as is desirable for mitotane or trilostane treatment, would be inappropriate and unexpected during selegiline treatment, dogs adequately treated with selegiline should not over-secrete cortisol. In contrast, two dogs in this study that were not initially hyperresponsive to tetracosactrin had become so by day 90. One dog with consistently high 1-hour cortisols (greatly exceeding group mean and median values at days 0, 10 and 30) was excluded from the mean 1-hour cortisol calculation at 90 days, but even so, an upward trend in mean 1-hour cortisols remained during the course of the treatment. These results clearly suggested that selegiline had no useful effect in controlling endocrine abnormalities in these dogs, as measured by cortisol response to tetracosactrin, UCCR or endogenous ACTH concentrations.

In a previous study on selegiline[2] great reliance was placed on assessment of subjective data such as water intake and other signs reported by owners. Consequently, in our study, owners were asked to complete a questionnaire to assess subjective signs and report any adverse reactions to the drug. Initially the subjective response appeared good, with 64% of dogs reported to have overall improvement at 10 days, though this decreased to 45% by 90 days. Most of the improvement was attributable to increased activity and improved demeanour, and only 1/11 had consistent improvement in more than one clinical sign during the trial, yet without noticeable physical changes over the 90 day trial period. Interestingly, this dog's baseline cortisol concentration decreased considerably, although adrenal responsiveness remained essentially unchanged and endogenous ACTH concentration increased over the 90 days.

In our study, the predominant clinical improvement reported by owners was in mental function and physical activity. It is thought that selegiline has a beneficial effect in dogs with age-related cognitive decline,[27] and it is possible that the response reported was an effect of selegiline on cognitive function or other ageing-related behaviour. Alternatively, active metabolites of selegiline such as amphetamine and phenylethylamine, which are both CNS stimulants, may have increased activity levels, and contributed to the owners' perception of general well-being. It has been argued that, at standard selegiline dosages, plasma and brain concentrations of these metabolites would be unlikely to have an observable effect on the dogs' behaviour.[16] However it is conceivable that low concentrations could have had subtle effects apparent to diligent pet owners closely observing a single, familiar dog, but not easily recognised in institutionalised laboratory dogs.

The reported reduction in water intake in some dogs at some time points might be attributable to a partial effect of the drug in treating PDH or may have been due to an effect on psychogenic aspects of polydipsia in affected dogs. The reasons for polyuria and polydipsia in PDH dogs is not fully understood. Although an effect of cortisol on renal tubular concentrating ability or a central diabetes insipidus is most often proposed as the mechanism,[22] it is conceivable that, as in people,[28] there are psychological effects of hypercortisolaemia, one of which might be psychogenic polydipsia. Indeed, some veterinary endocrinologists have proposed just such a mechanism (DB Church, unpublished observation).

Another possible influence was that owners were aware they were participating in a clinical trial to assess the efficacy of a new treatment. While the necessity for objective and accurate assessments was impressed upon the owners, only a placebo drug in a control group of animals could completely eliminate the possibility of placebo effect on the owners. This study was concurrent with a trilostane efficacy study,[29] and because of the potentially lethal consequences of untreated PDH, it was considered unethical to

have an untreated control group when all owners had elected to treat their PDH affected dog. On balance, with careful questioning and repeated re-phrasing of questions, we were reasonably satisfied that owners were giving a genuine and truthful account of their dogs' progress at home during treatment.

As in other studies there were no adverse effects attributable to selegiline at this dose rate (2 mg/kg/day). Owners reported occasional diarrhoea or vomiting but this did not persist or necessitate cessation of treatment, and these signs were not thought to be necessarily associated with selegiline treatment. These events may not have been any more frequent than in normal dogs.

It is of concern that of eleven treated dogs, four were dead within a month of completing the 90 day treatment (one before and three after) and a fifth dog died within 3 months. In at least three deaths persistence of PDH as a result of treatment failure may have contributed to mortality.

In nine of ten dogs that completed the selegiline study and were treated subsequently with mitotane, PDH was managed successfully: the other was euthanased 1 week into treatment. Success was confirmed by resolution of PDH signs and suppressed responses to stimulation testing (baseline and 1-hour cortisol concentrations <125 nmol/L), indicating that these dogs were not resistant to effective treatment.

Conclusions

Selegiline was confirmed as a safe drug with no important side-effects in dogs but was not effective for treating canine PDH at the dose used in this study. Due to the availability of other more reliable treatments, it cannot be recommended for treating this disease in dogs. In some dogs, selegiline may have an effect in increasing the activity levels and general alertness, possibly reflecting dopaminergic effects on the brain unrelated to treatment of PDH. It is conceivable that dogs with known pars intermedia tumours could respond better to selegiline, but premortem identification of tumour location in animals is not possible at present with imaging modalities available.

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