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Assessment of cabergoline as a reproductive inhibitor in coyotes (*Canis latrans*)

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The efficacy of three oral formulations (gelatin capsule, tablet, oil base) and five dosages (50, 100, 250, 500, 1000 μg) of cabergoline to disrupt reproduction in coyotes (*Canis latrans*) was evaluated. The type of formulation used had no effect on plasma progesterone and prolactin concentrations or on mean litter size. No adverse side effects (for example, vomiting, anorexia, diarrhoea) were observed despite the use of doses of up to 20 times the therapeutic dose used for domestic dogs and cats. All coyotes treated with 50, 100, 250 and 500 μg cabergoline whelped, but plasma progesterone concentrations in these coyotes were lower ($P \leq 0.07$) than in control animals at day 7 after treatment. Ten of 11 females treated with 1000 μg cabergoline whelped, but progesterone concentrations in these coyotes were lower than in control animals up to day 14 after treatment ($P \leq 0.04$). Dosages of 1000 μg cabergoline decreased blood serum prolactin ($P \leq 0.10$) and progesterone ($P \leq 0.06$) concentrations, but apparently failed to decrease progesterone below the threshold necessary to maintain pregnancy in all but one animal. However, progressive inhibition of prolactin and progesterone with increasing doses of cabergoline indicated that higher dosages might be effective in coyotes. Survival of pups born to cabergoline-treated females was not different ($P < 0.001$) from that of pups born to control females, but mean litter size was smaller for females treated with cabergoline ($P \leq 0.073$) than for the control females. Although all cabergoline treatments in this study were ineffective at preventing reproduction in coyotes, progressive inhibition of prolactin and progesterone with increasing dosages of cabergoline indicates that higher doses might be effective in preventing reproduction in coyotes. However, the physiological differences from other canine species in dopamine D2 receptors and mechanisms of luteal support may ultimately prevent the use of cabergoline for reproductive control in coyotes.

Introduction

Coyotes (*Canis latrans*) are one of the most widely distributed predators in North America (Bekoff and Wells, 1980) and depredation of domestic livestock by coyotes has been, and

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continues to be, a serious threat to animal production in the western USA. A number of both wild and domestic species, such as cattle, deer and antelope, can experience losses due to coyotes, but depredation of sheep is most economically significant, resulting in annual losses estimated at $17.7 million (US Department of Agriculture, 1995).

Losses incurred by coyotes on livestock have traditionally been managed by lethal means, such as aerial hunting, trapping and poisoning (Kirkpatrick and Turner, 1985). The effectiveness of these techniques is variable and dependent on environmental conditions, terrain, coyote density, and the magnitude and nature of the problems (Knowlton *et al.*, 1999). Recently, there has been increased public resistance and criticism of these traditional control methods. Thus, for the successful resolution of depredation problems, producers and resource managers need to incorporate a variety of techniques that integrate social, ethical and economic concerns, as well as the biology of the species, in the development of management strategies.

The use of reproductive intervention strategies as a means for reducing human–wildlife conflicts has re-surfaced in recent years (DeLiberto *et al.*, 1999). Application of such strategies to predators will probably be considered a humane alternative to lethal control, particularly if it preserves social structure and minimizes impact to non-target species.

In their breeding pair hypothesis, Till and Knowlton (1983) suggested that reproductive control in coyotes would be effective at reducing depredation of sheep. They indicated that many depredation problems caused by coyotes are from territorial adults providing for their young. These adult coyotes switch from feeding principally on small and medium prey, to killing larger species such as lambs. Till and Knowlton (1983) assumed that territorial breeders are the principal killers of livestock, and that depredations were linked to the presence of pups. In a field test of this hypothesis, Bromley and Gese (2001) demonstrated that coyote packs that had undergone tubal ligation and vasectomy maintained territories and predated on sheep less than did unaltered packs. Their work indicates that the development of reproductive inhibition techniques for coyotes that do not interfere with territorial behaviour would be valuable in reducing predation on sheep.

Experiments on reproductive inhibition in coyotes have been conducted, but there have been problems associated with an effective delivery system for most compounds studied (DeLiberto *et al.*, 1999). If effective in coyotes, cabergoline may have potential use in controlling reproduction by circumventing this problem. Cabergoline is an ergot derivative that acts as a dopamine agonist, resulting in a prolonged effect of reducing prolactin concentration. Cabergoline has fewer or no side effects, is relatively species specific, and is currently available in an oral form.

Studies have demonstrated that prolactin is an essential luteotrophic hormone in domestic dogs and cats, and in red foxes (*Vulpes vulpes*) and silver foxes (*Vulpes vulpes fulva*) (Concannon *et al.*, 1987; Post *et al.*, 1988; Okkens *et al.*, 1990; Valberg and Mondain-Monval, 1992; Onclin *et al.*, 1993; Jöchle, 1997). Therefore, compounds such as cabergoline that inhibit prolactin secretion cause regression of the corpora lutea and a subsequent decrease in circulating progesterone, ultimately resulting in the termination of pregnancy (Concannon *et al.*, 1987; Post *et al.*, 1988; Okkens *et al.*, 1990, 1993; Jöchle and Jöchle, 1993; Lengwinat *et al.*, 2001; Marks *et al.*, 2001). The aim of the present study was to evaluate the use of cabergoline as an effective reproductive inhibitor in coyotes. Five doses of cabergoline in three formulations administered during the last two stages of pregnancy were evaluated.

Materials and Methods

Study site, animals and general procedures

Studies were performed at the United States Department of Agriculture (USDA) National Wildlife Research Center (NWRC), Predation Ecology and Behavior Field Station (Millville,

UT). The NWRC, Institutional Animal Care and Use Committee approved all procedures in this study as protocol QA-691. Experiments were conducted between 1999 and 2001 using adult coyotes (3–8 years old), 9–11 kg body weight, which were obtained from the captive breeding colony at the Field Station. All animals used in this study had established breeding histories at the Station. The animals were born and raised by staff to minimize stress from routine handling and blood collection procedures.

In December of each year, male and female coyotes were placed in 0.1 ha pens and allowed to form pair bonds before the onset of oestrus in late January. Two open-sided shelters (0.75 m × 1.00 m) were provided in each pen for shade, and breeding pairs had access to an insulated den box (1.0 m diameter) with corn cob bedding. Coyotes were fed a daily ration consisting of meat slurry, and water was provided *ad libitum*.

Breeding and mating behaviours were documented by observers inside a building located between 300 m and 500 m from the pens. In Expt 1, pregnancies were confirmed by abdominal palpation 28–35 days after the first copulation. In Expts 2 and 3, pregnancies were verified by the detection of the pregnancy-specific hormone, relaxin, in blood plasma, using a commercially available ELISA for canines (REPROCHECK®; Synbiotics, Inc., San Diego, CA), validated for use in coyotes (Carlson and DeLiberto, 2001). Gestation in coyotes is about 62–66 days, similar to that in domestic dogs (Concannon *et al.*, 1983). Coyote pairs were maintained in breeding pens for at least 1 month after their expected whelping date (that is, late March–April) on the basis of the first observed copulation.

Treatments

Expt 1 was conducted in 1999 by randomly assigning pregnant female coyotes and their mates to 50 ($n = 5$) or 100 µg ($n = 3$) cabergoline treatment groups or to a control group ($n = 6$). In each treatment group, cabergoline (Galastop®; Jansen-Cilag, Neuss) was administered for 7 consecutive days starting on days 38–42 of gestation. Cabergoline was administered orally by mixing the compound in the daily food ration.

Expt 2 was initiated in 2000 by assigning 18 pregnant female coyotes and their mates to 250 and 500 µg cabergoline treatment groups and to a control group ($n = 6$ female coyotes per group). Female coyotes in each treatment group were given cabergoline in tablet form (Dostinex®; Pharmacia Corp., Peapack, NJ) for 7 consecutive days starting on days 32–38 of gestation. Cabergoline was administered by placing tablets in the posterior portion of the oral cavity and ensuring that the animals swallowed the dose. Control animals were handled in the same manner as cabergoline-treated coyotes, except that all animals received an empty gelatine capsule.

A third experiment was performed in 2001 to evaluate the effects of 1000 µg cabergoline administered in three different formulations. Pregnant females were assigned to the following treatments: (i) cabergoline administered in gelatin capsules ($n = 3$); (ii) cabergoline in tablet form (Dostinex®; $n = 5$); and (iii) cabergoline in fractionated coconut oil ($n = 6$). All formulations were administered by placing the dose into the posterior portion of the oral cavity and ensuring that the animals swallowed the dose. Treatments were administered for 7 consecutive days starting on days 32–38 of gestation.

Hormone and cabergoline analyses

In all experiments, blood samples were obtained by cephalic venepuncture from coyotes immediately before treatment, and at days 3, 7 and 14 after the first dose. Samples were centrifuged at 900–1000 ***g*** for 15 min and the supernatant was removed and frozen at –20°C. In Expt 1, progesterone in the blood was determined quantitatively using Coat-A-Count®

radioimmunoassay kits (Diagnostic Products Corporation, Los Angeles, CA) validated for use in dogs (Srikandakumar *et al.*, 1986; Willard *et al.*, 1986). We validated the assay for use in coyotes using two techniques. Recovery of progesterone in sera collected from female coyotes during anoestrus and spiked with either 2 or 19 ng progesterone ml^{-1} was 95 and 100%, respectively. This serum was also spiked with the kit standards (1:1 dilution) in a test for linearity that yielded a 0.995 correlation. A test for parallelism on four coyote serum samples diluted 1:32 yielded recoveries from 95 to 101%. The intra- and interassay coefficients of variation for analysis of experimental samples were 5.1 and 5.6%, respectively, within the range of 1–40 ng ml^{-1}.

In Expts 2 and 3, blood serum concentrations of progesterone were determined quantitatively using radioimmunoassay techniques described by Niswender (1973). The intra- and interassay coefficients of variation were < 0.78 and 6.47%, respectively. Progesterone concentrations on days 2, 7 and 14 in all experiments were calculated as a percentage change from pretreatment concentrations for all coyotes.

Prolactin assays were not determined for the 50 and 100 μg cabergoline treatments because an appropriate assay was unavailable during Expt 1. Blood serum concentrations of prolactin were determined in coyotes during Expts 2 and 3 on days 2, 7 and 14 by the Colorado State University (Animal Reproduction and Biotechnology Laboratory, Fort Collins). Radioimmunoassay for prolactin used a highly purified canine prolactin antigen for iodination AFP2451B, canine prolactin reference preparation and anti-canine prolactin (guinea-pig) antiserum AFP1062091GP obtained from the National Hormone and Pituitary Program, National Institute of Diabetes and Digestive and Kidney Disease at the National Institutes of Health. The intra- and interassay coefficients of variation were < 6.47 and 4.01%, respectively. Prolactin concentrations were calculated as a percentage change from pretreatment concentrations.

Blood plasma concentrations of cabergoline were determined using electrospray ionization tandem mass spectrometry (Kimball *et al.*, 2001). The recent development of this quantitative method allowed for measurement of cabergoline concentrations in Expt 3 only.

Statistical analysis

ANOVA was used to evaluate the effects of cabergoline treatments on litter size. Concentrations of serum progesterone and prolactin, and plasma cabergoline were evaluated with repeated measures ANOVA. Fisher's least significance difference tests were used to compare treatment means, when ANOVA detected differences among effects using a type I error rate of $\alpha = 0.10$.

Results

Litter size

All coyotes that received 50, 100, 250 or 500 μg cabergoline and all control animals whelped. In addition, all animals administered 1000 μg cabergoline in gelatin capsules and tablets also whelped. Only one of six coyotes that received 1000 μg cabergoline oil-based treatment failed to whelp. This animal was observed with a bloody vaginal discharge on day 6 of treatment (approximately day 38 of gestation).

No difference was observed in litter size among the three formulations of 1000 μg cabergoline. Consequently, these data were analysed as one treatment. Mean litter size in control animals was higher ($P \leq 0.07$) than in all treatment groups (Table 1).

Hormone and cabergoline analyses

Progesterone concentrations in all but two coyotes were maintained above 4 ng ml^{-1}. No significant difference was observed in mean percentage change of progesterone concentrations

Table 1. Mean litter size of female coyotes (*Canis latrans*) that received one of five oral dosages of cabergoline on 7 consecutive days during the last two phases of pregnancy

Treatment	*n*	Litter size (mean ± SD)
Control	12	6.7 ± 1.51[a]
Cabergoline (μg)		
50	5	3.6 ± 1.67[b]
100	3	4.3 ± 2.08[b]
250	6	3.8 ± 1.72[b]
500	6	4.0 ± 1.10[b]
1000	11	3.8 ± 1.93[b]

[ab]Values with different superscripts are significantly different ($P < 0.05$).

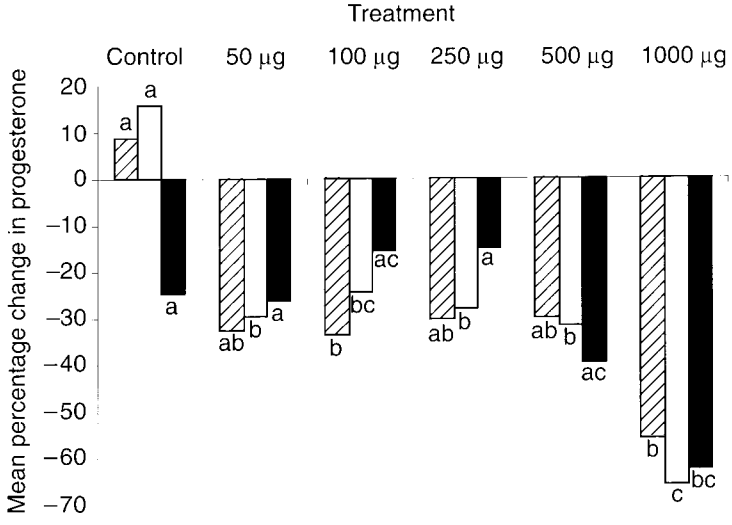

Fig. 1. Mean percentage change of serum progesterone concentrations in female coyotes (*Canis latrans*) at day 3 (▨), day 7 (□) and day 14 (■) after oral administration of one of five dosages of cabergoline. Animals treated with 50 and 100 μg cabergoline were treated between day 38 and day 49 of gestation. Coyotes treated with 250, 500 and 1000 μg cabergoline were treated between day 32 and day 40 of gestation. [abc]Bars within days with different letters are significantly different ($P < 0.10$).

from pretreatment concentrations among the three formulations of 1000 μg cabergoline. Consequently, these data were combined and analysed as one treatment. By day 3 of the treatment period, progesterone concentrations were lower than pretreatment concentrations for all treatment groups (Fig. 1). However, only mean percentage changes in progesterone concentrations in coyotes treated with 100 and 1000 μg cabergoline were significantly different from those of the control animals ($P \leq 0.04$). By day 7, decreases in progesterone concentrations were higher in all treatment groups ($P \leq 0.06$) than in the control animals, and the greatest decrease was observed in the 1000 μg cabergoline group ($P \leq 0.01$). Differences between control and treatment groups persisted for only the 1000 μg cabergoline group at day 14 ($P \leq 0.02$).

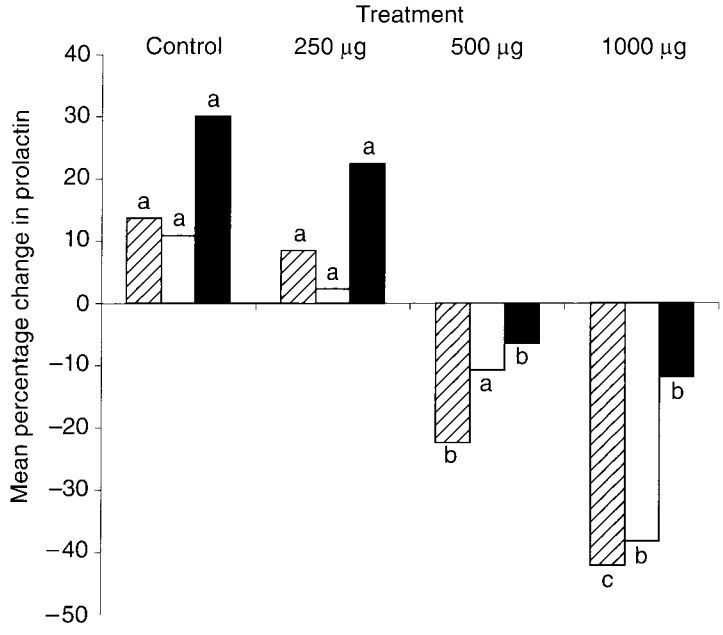

Fig 2. Mean percentage change of serum prolactin concentrations in female coyotes (*Canis latrans*) at day 3 (▨), day 7 (□) and day 14 (■) after oral administration of one of five dosages of cabergoline. Animals treated with 50 and 100 µg cabergoline were treated between day 38 and day 49 of gestation. Coyotes treated with 250, 500 and 1000 µg cabergoline were treated between day 32 and day 40 of gestation. ^{abc}Bars within days with different letters are significantly different ($P < 0.10$).

No significant difference was observed in the mean percentage change of prolactin concentrations from pretreatment concentrations among the three different formulations of 1000 µg cabergoline. Consequently, these data were combined and analysed as one treatment. Mean changes in prolactin concentrations did not differ between the control group and 250 µg cabergoline group at any sample period (Fig. 2). No decreases in prolactin from pretreatment concentrations were observed during any of the periods in either of these groups.

Decreases in prolactin were observed during all sample periods in the 500 and 1000 µg cabergoline treatment groups (Fig. 2). Mean percentage changes in prolactin concentrations for the 500 µg cabergoline treatment group were different from the control group ($P \leq 0.04$) and the 250 µg cabergoline treatment group ($P \leq 0.10$) at day 3 and day 14.

The greatest decreases in prolactin were observed in animals treated with 1000 µg cabergoline. Mean percentage changes in prolactin in this group were different from the control group ($P \leq 0.01$) and the 250 µg cabergoline treatment group ($P \leq 0.03$) at all sample periods. Differences were also observed between the 500 and 1000 µg cabergoline groups at day 3 ($P = 0.10$) and day 7 ($P = 0.04$), but these differences did not persist up to day 14.

Mean plasma concentrations of cabergoline were not different among animals treated with the three formulations of 1000 µg cabergoline. Consequently, data were combined and a single mean value was calculated for each time period. Plasma concentrations of cabergoline increased throughout the first 14 days after treatment (Fig. 3). From day 14 to day 42 after

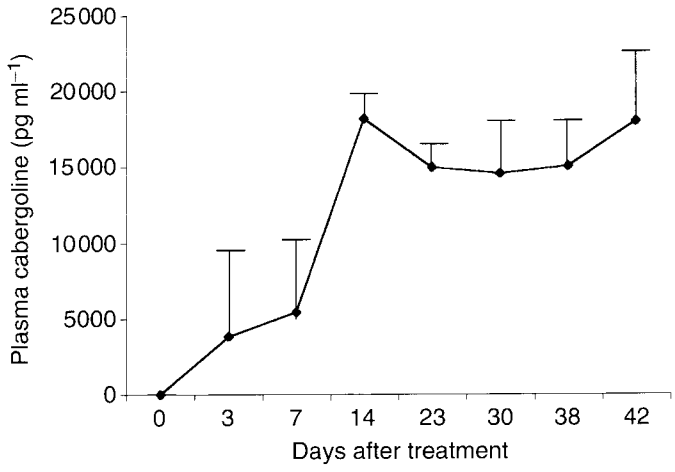

Fig 3. Mean plasma cabergoline concentrations in female coyotes (*Canis latrans*) after oral administration of 1000 μg cabergoline for 7 consecutive days between day 32 and day 40 of gestation.

treatment (that is, about 36 days of gestation up to 12 days after whelping), cabergoline concentrations stabilized between 14 480 and 18 125 μg ml^{-1}.

Expt 3 produced the only instance in which progesterone concentrations of a pregnant coyote were consistently below 4 ng ml^{-1} and failed to whelp. Treatment with 1000 μg cabergoline caused marked decreases in mean prolactin and progesterone concentrations. Mean percentage changes in prolactin concentrations of –42.1, –38.2 and –11.8 at days 3, 7 and 14, respectively, resulted in corresponding decreases in progesterone concentrations of –55.6, –65.7 and –62.3%, respectively. All of these decreases were different from those in control animals, but were only sufficient in the individual that failed to whelp. It is likely that a threshold of progesterone similar to that of other canine species (that is, 2 ng ml^{-1}) is required for the maintenance of pregnancy in coyotes (Concannon and Hansel, 1977; Johnston *et al.*, 2001). Only two animals had progesterone concentrations approaching this threshold. In one animal there was a decrease in progesterone concentrations from 46.5 ng ml^{-1} before treatment to 2.7, 6.9 and 10.7 ng ml^{-1} at days 3, 7 and 14 after treatment, respectively (Fig. 4b). This individual whelped four puppies at about day 62 after the first observed copulation. The progesterone concentrations of the second animal decreased from 32.1 ng ml^{-1} before treatment to 3.8, 2.5 and 3.22 ng ml^{-1} at days 3, 7 and 14 after treatment, respectively (Fig. 4a). This decrease and maintenance of progesterone concentrations below 4 ng ml^{-1} probably resulted in termination of pregnancy. Furthermore, if coyotes are similar to other canines, it is likely that progesterone concentrations in this animal decreased below 2 ng ml^{-1}. The inability to detect a decrease in progesterone below 2 ng ml^{-1} in the present study was probably a consequence of the sampling design; daily blood sampling may have been necessary to detect a decrease below threshold.

Discussion

Although all animals treated with cabergoline in Expt 1 whelped, endocrine data indicate that higher doses might have been effective. Mean progesterone concentrations for animals treated with 50 μg cabergoline were lower than in control animals at day 7, and for animals treated

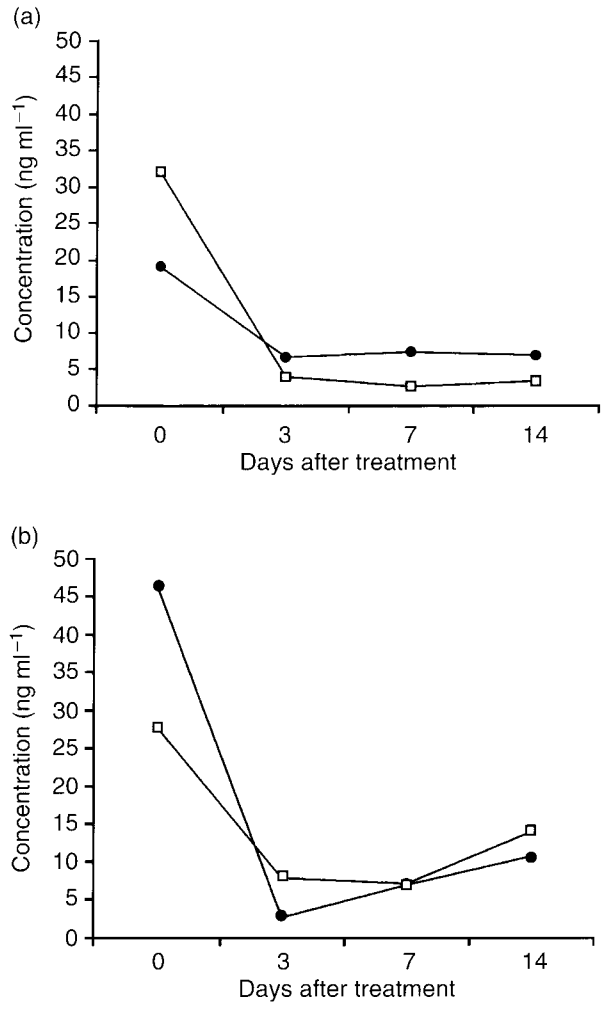

Fig 4. (a) Concentrations of prolactin (□) and progesterone (●) in a pregnant female coyote (*Canis latrans*) that failed to whelp after two treatments of 1000 μg cabergoline. (b) Concentrations of prolactin (□) and progesterone (●) in a pregnant female coyote that whelped after two treatments of 1000 μg cabergoline.

with 100 μg cabergoline at day 3 and day 7. Progesterone concentrations in these animals were also consistently lower than pre-dose concentrations. These data indicate that inhibition of pituitary prolactin secretion was insufficient to maintain an adequate suppression of luteal progesterone secretion below 4 ng ml^{-1}. Thus, the dose of cabergoline was increased in Expt 2, in an attempt to reduce progesterone concentrations below this threshold. However, administration of 250 and 500 μg cabergoline too was ineffective at terminating pregnancy in all coyotes. Progesterone concentrations in this experiment failed to decrease below the threshold that is thought to be necessary for the maintenance of pregnancy. Mean progesterone concentrations in coyotes treated with 250 and 500 μg cabergoline were not different from progesterone concentrations observed in the 50 and 100 μg treatment groups in Expt 1.

Although the pattern of progesterone suppression appeared to be similar in animals treated with 50, 100 and 250 μg cabergoline (that is, a gradual trend toward pretreatment concentrations from day 3 to day 14), the pattern was apparently reversed in animals treated with 500 μg cabergoline. In this treatment group, mean progesterone concentrations tended to decrease up to day 14, indicating a prolonged effect of cabergoline. Thus, it appeared that therapeutic doses of cabergoline had not been administered in Expts 1 and 2, and Expt 3 was initiated to evaluate 1000 μg cabergoline, a dose about 20 times the therapeutic dose used for domestic dogs and cats (Post *et al.*, 1988; Onclin and Verstegen, 1996).

Failure of all doses of cabergoline to terminate pregnancy in all but one animal leaves little doubt of the ineffectiveness of this compound in coyotes at dosages of up to 20 times the therapeutic dose used in domestic dogs and cats, and in red and silver foxes (Post *et al.*, 1988; Onclin and Verstegen, 1996; Lengwinat *et al.*, 2001; Marks *et al.*, 2001). The present study demonstrates that there are basic physiological differences among coyotes and other carnivores. Four potential differences are: (i) that the digestive physiology of coyotes interfered with gastrointestinal absorption of cabergoline; (ii) that the dopamine D2 receptors in the anterior pituitary of coyotes had lower affinity for cabergoline than in other carnivores; (iii) that alternative sources of prolactin or progesterone are present in coyotes; and (iv) that unlike in other carnivores, prolactin was not a luteotrophic agent in coyotes.

It is unlikely that the digestive physiology of the coyote interfered with the absorption of metabolically active cabergoline. Blood plasma analysis in Expt 3 revealed the presence of cabergoline by day 3 of treatment, showed an increase at day 7 and reached a plateau by day 14, which was maintained throughout whelping. These cabergoline concentrations are consistent with those reported in humans that received 36–85 μg kg^{-1} (Persiani *et al.*, 1992).

Therapeutic decreases in prolactin of 12.0–96.8% after administration of 5–50 μg cabergoline kg^{-1} have been reported in other species (Negishi and Koide, 1997; Onclin and Verstegen, 1997; Lengwinat *et al.*, 2001). Decreases in coyote prolactin concentrations of 6–42% were achieved only after treatment with 50 and 100 μg cabergoline kg^{-1}, indicating that dopamine D2 receptors in coyotes have a lower affinity for cabergoline than they do in other species. A genetic link between affinity for cabergoline and dopamine D2 receptors may also occur in wolves. Therapeutic doses of cabergoline in wolf–dog hybrids (15 μg kg^{-1}) and wolves (25 μg kg^{-1}) were three and five times higher than those in domestic dogs, respectively (J. P. Verstegen, personal communication). If interspecific differences in D2 receptor biology occur, higher doses of cabergoline may produce decreases in plasma prolactin concentrations that are sufficient to decrease progesterone below the threshold for maintaining pregnancy. Alternatively, other ergot derivatives (for example, bromocriptine) may have greater affinities for dopamine D2 receptors and, if so, may be more suitable for terminating pregnancy in the coyote.

It is important to note that cases of mis-mothering or unsuccessful nursing of litters by coyotes were not observed in any of the treatment groups. In fact, pup survival was not different between cabergoline-treated and control animals, despite the relatively large decreases in prolactin concentrations in animals treated with 1000 μg cabergoline, and a maintenance of relatively high concentrations of plasma cabergoline throughout whelping. In pseudopregnant and lactating domestic bitches, treatment with 5 μg cabergoline kg^{-1} rapidly causes cessation of lactation (Jöchle *et al.*, 1989). In cats treated with 5 μg cabergoline kg^{-1} after day 42 of pregnancy, preparations for lactation were inhibited and kittens born prematurely or at term could not be nursed but died quickly (Jöchle and Jöchle, 1983).

Furthermore, no adverse side effects (for example, vomiting and anorexia) were observed in any of the coyotes during the experiments despite the fact that doses of up to 20 times those used in dogs and cats were administered. Previous research on domestic dogs and cats

demonstrated such side effects with much lower doses of cabergoline (Post *et al.*, 1988; Jöchle *et al.*, 1989; Onclin and Verstegen, 1996). This observation, combined with the apparent difference in the effect of cabergoline on lactation between coyotes and domestic animals, provides further evidence for the insensitivity of coyotes to the compound.

Administration of higher doses of cabergoline may fail to decrease sufficiently prolactin or progesterone if alternative sources of these hormones are present in coyotes. Such sources may include the fetoplacental unit. It was possible that by day 14 after administration of the first dose (that is, about day 46 of gestation), maintenance of pregnancy was under complete or partial control of the placenta. A transfer of placental support has been documented in domestic cats. Cabergoline was efficacious in domestic cats only when administered between day 28 and day 42 of gestation (Jöchle *et al.*, 1989; Verstegen *et al.*, 1993). Before day 28, placental support was thought to be multi-factorial. After day 42, progesterone produced by the placenta was sufficient to maintain pregnancy. However, in domestic dogs, the placenta does not appear to be capable of synthesizing large amounts of progesterone (Kiso and Yamauchi, 1984). Unfortunately, only limited information on the reproductive physiology of coyotes is available, and the mechanisms of placental support have not been identified.

Although the last three hypotheses may have influenced the effectiveness of cabergoline, it is also possible that hormones other than prolactin contributed to the maintenance of corpora lutea. Concannon (1980) and Concannon *et al.* (1987) proposed that LH was luteotrophic during the first phase of pregnancy in domestic dogs; prolactin became luteotrophic about mid-way through the second stage of pregnancy. Significant reductions in circulating progesterone concentrations observed in the present study indicate that cabergoline treatments negatively affected corpora lutea; smaller litter sizes in cabergoline-treated than in control coyotes supported this conclusion. Thus, prolactin may have provided only partial support for corpora lutea.

In domestic dogs, it is generally accepted that prolactin is the main, if not the only, luteotrophic factor. Concannon *et al.* (1987) demonstrated depression of luteal progesterone secretion by administration of anti-LH serum and by bromocriptine, thereby providing evidence for at least two luteotrophins in domestic dogs. However, when LH was suppressed by administration of a gonadotrophin-releasing hormone agonist, progesterone secretion was not affected, indicating that LH is not the primary luteotrophic factor (Okkens *et al.*, 1990). Unfortunately, the role of low LH concentrations on luteal function has not been elucidated.

The specific role of LH and prolactin in maintaining progesterone concentrations throughout pregnancy in coyotes remains unclear. LH may play a more important role in maintaining luteal function and, consequently, the maintenance of pregnancy in coyotes than in domestic dogs. We are currently comparing LH concentrations in non-pregnant and pregnant animals. In addition, evaluation of LH concentrations in coyotes treated with cabergoline is also being conducted.

Although disruption of reproduction was successful in only one coyote, the present study indicates that higher dosages of cabergoline might be effective. For example, litter sizes were 36–44% lower in cabergoline-treated females than in control animals. It is possible that this decrease was due to cabergoline and not to an artefact of the methodology. All coyotes were raised at the Field Station and received extensive handling before the initiation of the study. In addition, control coyotes were handled in the same manner as treatment animals, except that they were given placebos. Finally, the reduction in litter sizes in carbergoline-treated animals was observed during the three breeding seasons in which the experiments were conducted.

Progressive inhibition of prolactin and progesterone with increasing doses of cabergoline indicate that higher doses of cabergoline would have been effective in controlling reproduction. Future research should evaluate higher doses of cabergoline in pregnant coyotes. In addition,

elucidation of the mechanisms of luteal and placental support in coyotes will be invaluable in advancing our understanding of coyote reproductive physiology, and in designing and evaluating strategies for disrupting it.

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