Title
Evaluation of cabergoline as a reproductive inhibitor for coyotes (Canis latrans)

Permalink
https://escholarship.org/uc/item/69z232d8

Journal
Proceedings of the Vertebrate Pest Conference, 19(19)

ISSN
0507-6773

Authors
Seglund, Amy E.
DeLiberto, Thomas J.
Kimball, Bruce A.

Publication Date
2000

DOI
10.5070/V419110117
EVALUATION OF CABERGOLINE AS A REPRODUCTIVE INHIBITOR FOR COYOTES (CANIS LATRANS)

AMY E. SEGlund, and THOMAS DElIBERTO, USDA-APHIS, Wildlife Services, National Wildlife Research Center, Predation Ecology and Behavior Project, Utah State University, Logan, Utah 84322-5295.

BRUCE KIMBALL, USDA-APHIS, Wildlife Services, National Wildlife Research Center, 4201 La Porte Avenue, Fort Collins, Colorado 80521.

ABSTRACT: Cabergoline, a prolactin inhibitor, was evaluated on its potential use as a reproductive inhibitor for coyotes (Canis latrans). Groups consisting of six female coyotes were randomly assigned to three treatments and a control group. At 25 to 35 days after fertilization, coyotes were palpated to verify pregnancy status. If an animal was confirmed pregnant, it was dosed with 50 µg, 100 µg, or 250 µg of cabergoline, or a placebo for seven consecutive days on approximately day 40 of gestation. Five animals dosed with 50 µg of cabergoline, three dosed with 100 µg, and three animals receiving placebo whelped; no animals treated with 250 µg whelped. No drop in serum progesterone or prolactin levels were observed for the 50 µg and 100 µg treated groups. However, progesterone levels declined below 2 ng/ml in animals treated with 250 µg. Prolactin and progesterone levels in the control group followed typical patterns observed in pregnant canines. This study suggests that cabergoline is a potential reproductive inhibitor in coyotes. Future studies should determine if the efficacy of cabergoline in terminating pregnancy in coyotes could be improved with higher doses and at earlier stages of gestation.

KEY WORDS: cabergoline, Canis latrans, coyote, fertility control, pregnancy, prolactin, progesterone

(March 6-9, 2000, San Diego, California)

INTRODUCTION

Coyotes are one of the most widely distributed predators in North America (Bekoff and Wells 1986), and depredation by them on domestic livestock has been, and continues to be, a serious threat to producers in the western United States. A number of both wild and domestic species such as cattle, deer, and antelope can experience losses due to coyotes, but depredation on sheep is the most economically significant with yearly losses estimated at $17.7 million (U.S. Department of Agriculture 1995). Producers in the western U.S. suggest that problems by predators have risen in recent years and attribute this to an increase in predator numbers, less efficient methods for controlling predators, and ineffective management plans (American Sheep Industry Association 1999).

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 dependant on environmental conditions, terrain, coyote density, and the magnitude and nature of problems (Knowlton et al 1999). Recently, there has been increased public resistance and criticism of these traditional control methods. Thus, for the resolution of depredation problems to be successful, producers, and resource managers need to incorporate a variety of techniques that integrate social, ethical, and economical concerns, as well as the biology of the species, in the development of management strategies.

The use of fertility control as a means for reducing depredation problems has surfaced in recent years (DeLiberto et al. 1999). The use of this technique as a possible management tool represents an effective and humane alternative because it is non-lethal, predator social structure is preserved, territories are maintained, and non-target species can be protected. Another reason for the interest in reproductive inhibition is the breeding pair hypothesis developed by Till and Knowlton (1983). They indicated that many depredation problems caused by coyotes are from territorial adults provisioning for young. These adult animals switch from feeding principally on small and medium prey, to killing 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.

Experiments on fertility control have been conducted, but most compounds studied have had problems associated with an effective delivery system and a requirement for repeated doses (DeLiberto et al. 1999). Cabergoline is an ergot derivative that acts as a dopamine agonist, resulting in a prolonged prolactin-lowering effect. Cabergoline may have potential use in reproductive control because it has little or no side effects, is relatively species specific, is currently in an oral form, and has been shown to terminate pregnancy in the domestic dog (Onclin et al. 1993; Onclin and Versiegen 1997; Post et al 1988) and the red fox (Vulpes vulpes) (Marks et al. 2000).

The goal of our research was to evaluate the use of cabergoline as an effective reproductive inhibitor in coyotes. We examined three levels of cabergoline administered during the last trimester of pregnancy.

METHODS

Experiments were conducted at the USDA-Wildlife Services, National Wildlife Research Center’ Predation Ecology and Behavior Station in Millville, Utah. This facility provided a unique opportunity to study...
Twenty-four female coyotes were randomly assigned to three treatments and two control groups. Two of the treatment groups (n=6 females each) were housed in 0.1 ha pens and paired continuously with a male coyote. The third treatment group (n=6 females) was housed within individual kennels (4.3 m²). Males were paired daily with these females continually, except during feeding, for approximately two months. Two control groups consisting of three animals each were used. One control group was housed in 0.1 ha pens with a male coyote and the other control group was housed in the pens and paired daily with a male coyote.

Observations of mating behavior in the 0.1 ha pens were collected from sunrise to sunset seven days a week until all pairs completed breeding. These data were collected to evaluate mating behavior and document tie dates. At 28 days after the first observed tie, coyotes were palpated to evaluate pregnancy status. If an animal had a confirmed pregnancy, it was randomly placed into one of three treatment groups or a control group. Female coyotes were administered treatments for seven consecutive days beginning 40 days after the middle tie date. Treatments consisted of 50 µg (Group 1), 100 µg (Group 2), 250 µg (Group 3), and a placebo (Group 4). Doses of cabergoline were given in food. Animals housed in the larger pens received doses of an oily based formulation (Galastop: Centralvet, Milano) while those in kennels received a tablet formulation (0.5 mg tablet: Dostinex Tablets: Pharmacia & Upjohn).

Blood samples were obtained by cephalic veinipuncture. Blood was collected weekly until two weeks after the actual or predicted whelping date, and on day 3 and 7 during treatment. The blood samples were centrifuged for 20 min. at 1100 rpm within 2 hours after collection. The supernatant was isolated and stored at -20°C until analyzed.

Serum progesterone concentrations were run to examine treatment efficacy. Progesterone levels were estimated with a direct solid phase enzymeimmunoassay for the quantitative determination of progesterone using an ELISA kit validated for dog serum (American Laboratory Products Company, LTD., Windham, NH).

Serum prolactin concentrations were run only for pregnant females, based on whelping information and progesterone levels, in the 100 µg and 250 µg treatment groups, and for the control group. Prolactin levels were estimated with an enzyme immunometric assay designed for the quantitative measurement of prolactin in canine serum (the Milenia® Canine Prolactin, American Laboratory Products Company, LTD., Diagnostic Products Corporation, Germany).

RESULTS

Five of the treatment animals in Group 1 successfully whelped young. Litter sizes ranged from 1 to 5 pups with an average of 3.6 pups. Three of the females in Group 2 whelped young with litter sizes ranging from 2 to 6 pups with an average of 4.3 pups. None of the females in Group 3 whelped. One female in Group 3 had tary feces on day 4 of treatment, which may have been an indication of abortion. Three of the control animals whelped young, two from the 0.1 ha pens and one in the kennels. The two control animals housed in the larger pens had litter sizes of 4 and 5 pups and the control animal in the kennel whelped 4 pups, an average of 4.3.

For the control, 50 and 100 µg groups there appeared to be a normal decline in progesterone associated with the progression of gestation (Figures 1, 2, 3 and 4). No significant drop in progesterone associated with the treatment of cabergoline was detected. For the 250 µg treatment group, progesterone declined on day 3 and 7 of treatment to below the 2.0 ng/ml. Research suggests that 2.0 ng/ml is the threshold level of progesterone necessary to maintain pregnancy in the domestic dog (Onclin et al 1993; Concannon and Hansen 1977). This is likely the reason these females failed to whelp. Progesterone concentrations did rebound slightly by the post-treatment blood draw.

Prolactin concentrations for the both the 100 µg and 250 µg treatment groups decreased during treatment, but rebounded within a week post treatment. However, the 250 µg treatment group did not rebound as dramatically by the post-treatment blood draw. Prolactin concentrations for the control group were lower on day 3 and 7 post-treatment, but remained stable throughout the remainder of the study.

Figure 1. Mean serum progesterone concentrations a week pretreatment, day 3 and 7 of treatment, and a week post-treatment of pregnant females (n=5) administered a seven consecutive day treatment of 50 mcg cabergoline starting on approximately day 40 of pregnancy.
Figure 2. Mean serum progesterone and prolactin concentrations a week pre-treatment, day 3 and 7 of treatment, and a week post-treatment of pregnant females (n=5) administered a seven consecutive day treatment of 50 mcg cabergoline starting on approximately day 40 of pregnancy.

Figure 3. Mean serum progesterone and prolactin concentrations a week pre-treatment, day 3 and 7 of treatment, and a week post-treatment of pregnant females (n=3) administered a seven consecutive day treatment of 50 mcg cabergoline starting on approximately day 40 of pregnancy.
Pregnancy and sheep after the first trimester, which consecutive day treatment of and canines luteotrophic support in mid to maintenance of the corpus luteum is essential concentrations a week pre-treatment, day 3 and 7 of treatment, the placental progesterone to maintain pregnancy). Consequently, all animals in Group 2 whelped. Evidence of a dose dependent response was reported in people (Mattei et al. 1988). They found that hyperprolactinemic patients that were administered a 0.6 mg dose of cabergoline had significant mean maximum decreases of prolactin over patients given a 0.3 mg dose. In addition, patients administered the 0.6 mg dose experienced continued depressed serum prolactin levels from 3 hours to 14 days, while the 0.3 mg dosage group had significant reductions in prolactin levels for only 3 hours to 5 days. Therefore, it is likely that our 50 µg and 100 µg doses were too low to be efficacious.

In Group 3, three animals refused to consume food that contained cabergoline after day 3 of treatment. Cabergoline may have caused the females to become ill and avoid the food and the associated dose. Such an aversion has been noted in domestic dogs (Jochle, pers. comm. 1999). However, these coyotes did not whelp, suggesting that the 250 µg treatment terminated pregnancy in these animals after only one to three doses.

In the red fox (Marks et al. 2000), cabergoline terminated pregnancy during mid gestation, but was unsuccessful later in gestation. Foxes treated twice with cabergoline prior to day 28 of gestation did not whelp. However, pregnancy was not reliably terminated in foxes treated after day 35 of gestation.

Timing of cabergoline administration may have played affected the results in our study. Determination of fertilization and pregnancy is difficult in coyotes. Although our experimental design consisted of initiating treatment on day 40 of gestation, we had no means of accurately determining fertilization. Coyote breeding records for the past 20 years at Predation Ecology and Behavior Center suggest that fertilization generally occurs between the first and middle observed tie dates. Thus, we conservatively estimated fertilization as the observed middle tie date to ensure that all animals had reached the stage of pregnancy whereby prolactin was luteotrophic. This strategy undoubtedly resulted in the initiation of treatment of some females after day 40 of pregnancy. Consequently, if there is a point in late gestation of coyotes when treatment with cabergoline becomes ineffective, it may explain why some of our treated animals whelped. However, this is unlikely because of our complete success in terminating pregnancy with 250 µg and the complete ineffectiveness with 50 and 100 µg of cabergoline.

DISCUSSION

In mammals, progesterone is indispensable for the maintenance of pregnancy (Hodgen and Itskowitz 1988). Any prolonged depression of serum progesterone levels below 2 ng/ml will result in termination of pregnancy (Csapo et al. 1972; Concannon and Hansel 1977; Lombardi 1998). In most mammals, this threshold level of progesterone secretion is accomplished by the corpus luteum (notable exceptions include primates throughout pregnancy and sheep after the first trimester, which utilize the placental progesterone to maintain pregnancy). Therefore, maintenance of the corpus luteum is essential for pregnancy.

Maintenance of the corpus luteum in most mammals is accomplished by luteinizing hormone secreted by the anterior pituitary gland. However, in rodents, felines, and canines luteotrophic support in mid to late pregnancy is provided by prolactin released from the anterior pituitary (Rothchild 1981; Concannon et al. 1987; Jochle 1997). Consequently, suppression of prolactin during pregnancy in these species will result in regression of the corpus luteum and, ultimately, termination of pregnancy.

Cabergoline suppressed prolactin levels in serum of pregnant coyotes in Groups 2 and 3. However, cabergoline only was successful in terminating pregnancy in Group 3 coyotes. These data suggest that the 50 µg dose considered adequate for treating domestic dogs was not effective in coyotes. Also, although the 100 µg dose resulted in a decrease in mean prolactin levels of coyotes in Group 2, it was apparently insufficient to cause mean serum progesterone levels to fall below the 2 ng/ml threshold for maintenance of pregnancy.

In all experiments, the results were significantly different between Group 1 (control) and Groups 2 and 3 (cabergoline treated) (Table 2). Coyotes treated with cabergoline from day 1 to 40 of pregnancy whelped, while coyotes treated only after day 40 of pregnancy did not whelp. Further, coyotes treated with cabergoline after day 28 of gestation did not whelp. Consequently, if pups are to be successfully terminated, the treatment has to be initiated prior to day 28 of pregnancy. In contrast, the Cabergoline may have caused the females to become ill and avoid the food and the associated dose. Such an aversion has been noted in domestic dogs (Jochle, pers. comm. 1999). However, these coyotes did not whelp, suggesting that the 250 µg treatment terminated pregnancy in these animals after only one to three doses.

In the red fox (Marks et al. 2000), cabergoline terminated pregnancy during mid gestation, but was unsuccessful later in gestation. Foxes treated twice with cabergoline prior to day 28 of gestation did not whelp. However, pregnancy was not reliably terminated in foxes treated after day 35 of gestation.

Timing of cabergoline administration may have played affected the results in our study. Determination of fertilization and pregnancy is difficult in coyotes. Although our experimental design consisted of initiating treatment on day 40 of gestation, we had no means of accurately determining fertilization. Coyote breeding records for the past 20 years at Predation Ecology and Behavior Center suggest that fertilization generally occurs between the first and middle observed tie dates. Thus, we conservatively estimated fertilization as the observed middle tie date to ensure that all animals had reached the stage of pregnancy whereby prolactin was luteotrophic. This strategy undoubtedly resulted in the initiation of treatment of some females after day 40 of pregnancy. Consequently, if there is a point in late gestation of coyotes when treatment with cabergoline becomes ineffective, it may explain why some of our treated animals whelped. However, this is unlikely because of our complete success in terminating pregnancy with 250 µg and the complete ineffectiveness with 50 and 100 µg of cabergoline.

322
We are continuing our research on cabergoline and its efficacy in coyotes. This year, female coyotes will be administered doses with 150 µg for seven days, 250 µg for seven days, or 500 µg for one day. The latter dose of cabergoline was selected to evaluate its potential if only one dose could be delivered in the field. Marks et al. (1996) used fox baits around dens that contained 170 µg of cabergoline. Dens were each treated once in August and once in September resulting in a significantly lower incidence of cubs.

In addition, we will be using a relaxin pregnancy test (Qualitative relaxin assay, Reprocheck, ELISA, Symbiotics Corp., San Diego, CA), as well as palpation to verify pregnancy status and to refine our estimate of fertilization date. The pregnancy test will be run 21 days after the first observed tie and will also be run daily during the treatment regime to determine if pregnancy has been terminated. Additionally, serum progesterone levels will also be used to determine the point during treatment that pregnancy was terminated. Such data will provide valuable information on the number of cabergoline doses required to terminate a pregnancy and the period of gestation during which treatments are effective.

CONCLUSIONS
Producers consider predation a major factor in the decline of the sheep industry (Buys 1975; Gee et al. 1977). Currently, the most effective means of resolving predation problems is through lethal control methods. Even though these strategies minimize losses to producers, coyotes can still cause significant economic hardship. Additionally, as human population expands into wildlife habitat, lethal control options become limited and controversial. Therefore, there is a need to develop non-lethal control strategies that can be integrated into wildlife damage management programs.

Development of cabergoline as a reproductive inhibitor may further decrease losses due to coyote depredation, making sheep producers throughout the United States more profitable and competitive. Initial studies on cabergoline and other reproductive inhibitors are encouraging. Continued research on alternative control methods such as cabergoline are critical for the survival of the sheep industry.

ACKNOWLEDGMENTS
This project would not have been possible without the dedication of Jessica Tegt, Cody Nielsen, Krista Wenning, Debra Carlson, and Sarah Rose who spent many long days handling, helping with blood draws, and caring for coyotes. We also are indebted to Dr. Wolfgang Jochle for all his helpful suggestions on study design and use of cabergoline. And finally, many thanks to Terrie Wierenga and the USDA-ARS Poisonous Plant Lab for conducting prolactin and progesterone assays.

LITERATURE CITED
AMERICAN SHEEP INDUSTRY. 1999. Sheep and predator management. Englewood, CO.
BECKOFF, M., and M. C. WELLS. 1980. The social ecology of coyotes. Sci. Amer. 242: 130-148.
BUYS, C. L. 1975. Predator control and ranchers’ attitudes. Envir. Behav. 7:81-89.
CONCANNON, P. W., P. WEINSTEIN, S. WHALEY, and D. FRANCK. 1987. Suppression of luteal function in dogs by luteinizing hormone antiserum and by bromocryptine. J. of Repro. Fert. 81: 175-180.
CONCANNON, P. W., W. R. BUTLER, W. HANSEL, P. J. KNIGHT, and J. M. HAMILTON. 1978. Parturition and lactation in the bitch: serum progesterone, cortisol and prolactin. Biol. Repro. 22: 438-442.
CSAPO, A. I., M. O. PULKKINEN, B. RUTTNER, J. P. SANVAGE, and W. G. WIEST. 1972. The significance of the human corpus luteum in pregnancy maintenance. I. Preliminary studies. Amer. J. Obstet. Gynecol. 112:1061.
DELIBERTO, T. J., M. R. CONOVER, E. M. GESE, F. F. KNOWLTON, J. R. MASON, L. MILLER, R. H. SCHMIDT, and M. K. HOLLAND. 1999. Fertility control in coyotes: Is it a potential management tool? Proceedings 18th Annual Vertebrate Pest Conference.
GEE, C. K., R. K. MAGLEY, D. B. NIELSON, and D. M. STEVENS. 1977. Factors in the decline of the western sheep industry. U.S. Dept. Agricul., Econ. Res. Serv., Agricul. Econ. Rep. 377. 31 pp.
HODGEN, G. D., and J.ITSKOVITZ. 1988. Recognition and Maintenance of pregnancy. Pages 1995-2021 in The physiology of reproduction, E. Knobil, and J. Neil, eds. Raven Press Ltd., New York.
JOCHLE, W. 1997. Prolactin in canine and feline reproduction. Reprod. Dom. Anim. 32:183-193.
KNOWLTON, F. F., E. M. GESE, M. M. JAEGGER. 1999. Coyote depredation control: an interface between biology and management. J. of Range Manag. 52:398-412.
KIRKPATRICK, J. F., and J. W. TURNER. 1985. Chemical fertility control and wildlife management. Biosci. 35(8):485-491.
LOMBARDI, J. 1998. Comparative vertebrate reproduction. Kluwer Academic Publishers. Boston, MA. 469 pp.
MARKS, C. A. et al. 2000. Control of red fox (Vulpes vulpes) fertility with cabergoline: dose response and intervention timing. In Press.
MARKS, C. A., N. N. NIJK, F. GIGIOTTI, F. BUSANA, R. V. SHORT. 1996. Preliminary field assessment of a cabergoline baiting campaign for reproductive control of the red fox (Vulpes vulpes). Wildl. Res. 3:161-168.
MATTEI, A. M., C. FERRARI, P. BAROLDI, V. CAVIONI, A. PARACCHI, C. GALPAROLI, C. ROMANO, D. SPELLECCHA, G. GEREVINI, and P. G. CROSIGNANI. 1988. Prolactin-lowering effect of acute and once weekly repetitive oral administration of cabergoline at two dose levels in hyprolactinemic patients. J. of Endocr. And Metab. 68(6) 1201-1206.
ONCIN, K., and J. P. VERSTEGEN. 1997. In vivo investigation of luteal function in dogs: effects of cabergoline, a dopamine agonist, and prolactin on progesterone secretion during mid-pregnancy and diestrus. Dom. Anim. Endocr. 14(1): 25-38.
ONCLIN, K., L. D. M. SILVA, I. DONNAY, and J. P. VERSTEGEN. 1993. Luteotrophic action of prolactin in dogs and the effects of a dopamine agonist, cabergoline. J. of Repro. Fert., Suppl. 47:403-409.

POST, K., L. E. EVANS, and W. JOCHLE. 1988. Effects of prolactin suppression with cabergoline on the pregnancy of the bitch. Theriogenology. 29:1233-1243.

ROTHCHILD, I. 1981. The regulation of the mammalian corpus luteum. Recent Prog. Horm. Res. 37:183.

TILL, J. A., and F. F. KNOWLTON. 1983. Efficacy of denning in alleviating coyote depredations upon domestic sheep. J. of Wildl. Manage. 47:1018-1025.

UNITED STATES DEPARTMENT OF AGRICULTURE. 1995. Sheep and goat predator loss. U.S. Department of Agriculture, National Agricultural Statistics Board, Washington, DC.