Control of reproductive success in rabbits using bromocriptine

Y.H. COTTAM, S.W. PETERSON AND S.N. McCUTCHEON

Department of Animal Science, Massey University, Palmerston North, New Zealand.

ABSTRACT

Feral rabbits impose a substantial environmental and economic cost in this country, causing pasture devastation over large areas of land, accelerating erosion and decreasing vegetation cover. Existing or potential methods of control have a high ethical cost, and there is a need to identify new methods of control. Manipulation of lactation, to enhance mortality and inhibit growth and development of the young, is a possible alternative strategy. Prolactin (PRL) is known to be important for establishment and maintenance of lactation in rabbits, and PRL secretion may be inhibited by administration of ergot alkaloids such as bromocriptine (CB154). These substances are orally active and so could potentially be used in baits. In order to determine whether CB154 could be used in baits, it is first necessary to establish the lowest effective dose. The objective of this study was to examine the relationships between dose of CB154 (initially administered systemically) and the growth and survival of kits. Sixteen pregnant New Zealand White does were divided into four treatment groups receiving different doses (mg/kg live weight/d) of CB154 ("low"(L), 0.2; "medium"(M), 0.4; "high"(H), 0.8; and control (C), 0). From day 3 of lactation, does were injected once daily with CB154 or excipient. Treatment continued until day 14 or until the death of all the kits, whichever came first. There were significant treatment effects on the proportion of kit deaths on all measurement days. By day 17, kit mortalities were: C, 20%; L 42%; M, 64%; H, 71%;)($P<0.05$). The weight gain of the surviving kits from day 3 to 8 did not differ significantly between treatment groups, but kit weight gain day from days 8 to 13 showed a significant treatment effect ($P<0.01$) (control, 83.7±11.4g; low, 18.7± 11.4g; medium, 33.5±17.2g; high -0.8±14.9g). Results are discussed in relation to the possible use of bromocriptine as a bait to control reproductive success, and to the fact that these rabbits were much less sensitive to bromocriptine than previously published studies would suggest.

Keywords: rabbits; bromocriptine; CB154; prolactin.

INTRODUCTION

Feral rabbits impose a substantial environmental and economic cost on this country, the latter estimated at a minimum of $22 million dollars annually in control costs and lost production (RBAG 1996). Existing methods of feral rabbit control have a high ethical cost and problems of public non-acceptance. Manipulation of lactation, to enhance mortality and inhibit growth and development of young, is a possible alternative strategy.

For many years, prolactin (PRL) has been known to be important for the establishment and maintenance of lactation in rabbits (Cowie *et al.* 1969; Falconer and Fiddler 1970). With rabbit lactation being PRL-dependent, the inhibition of PRL secretion in the dam is expected to abolish lactation. PRL secretion may be inhibited by administration of ergot alkaloids such as bromocriptine (CB154) (Buys *et al.* 1995), which acts as a dopamine receptor agonist. Furthermore, these substances are orally active (Cingotti and Magnin 1986; Okkens *et al.* 1990) and so could potentially be used in baits. While CB154 has been used experimentally to inhibit lactation in the rabbit (Cowie *et al.* 1969; Taylor and Peaker 1975; Fortun *et al.* 1994) these studies focused on the biology of lactation rather than control of a noxious pest.

Ultimately, there may be potential to develop an oral dose of bromocriptine in a pellet acceptable to rabbits, which could be aerially broadcast over wide areas. This could be used to control feral rabbit populations, without the introduction of diseases or recourse to use of poisons. In order to determine whether CB154 could be used in baits, it is first necessary to establish the lowest effective dose. The objective of this study was therefore to examine the relationships between dose of systemically administered CB154 and the growth and survival of kits.

MATERIALS AND METHODS

Sixteen mixed-age pregnant New Zealand White does were housed in individual pens with *ad libitum* access to pellets and fresh water. Once they had kitted, does were randomly assigned to one of four treatment groups: 'control', 'low', 'medium' and 'high' dose of bromocriptine (Table 1). Live weights of the does on day 3 of lactation ranged from 4.0 to 5.2 kg, and litter size from 3 to 12.

Bromocriptine (2-bromo-α-ergo-cryptine; B-2134, Lot numbers 33H1393 and 83H0799, Sigma Chemical Company, U.S.A) was dissolved in 60% ethanol and 40% saline, at concentrations shown in Table 1. Does received once-daily subcutaneous injections commencing at 0900h on day 3 of lactation. The injection site, in the posterior neck region, was prepared by liberal application of 70% ethanol, and injections were performed using a 25G needle. Doses were calculated on the basis of an injection volume of 0.05 ml per kg live weight, and volumes ranged from 0.20 to 0.26 ml. Does were re-weighed after 7 days of treatment, and their injection volumes adjusted accord-

ingly. Bromocriptine solutions were made up weekly and refrigerated between injections.

TABLE 1: The doses and concentrations of bromocriptine.

Treatment Group	Dose (mg/kg/day)	Concentration of each stock solution (mg/ml)
Control	0	0 [a]
Low	0.2	4
Medium	0.4	8
High	0.8	16

[a] Control animals were injected with 60% ethanol: 40% saline solution, at the same volume per kg body weight as treated animals.

MEASUREMENTS

Number of kits born in each litter (alive and dead) and date of kitting were recorded at birth. On the third day after kitting (day 1 of treatment), the live weight of each doe and total weight of kits in each litter were recorded. Does and kits were then weighed at kit ages 7, 8 or 9, and 12, 13 or 14 days of age. These groups will henceforth be referred to in terms of mean kit age, i.e., 8 and 13 days, respectively. The number of kits surviving per litter was noted daily at injection time. Injections continued until day 14 of lactation (i.e., day 11 of treatment), or until the death of all the kits in the litter, whichever came first. Until this time, the kits were solely dependent on the does' milk.

Litter size (at day 1 of treatment) was assigned to two litter-size groups (2-7 and 8-12 kits), and treated as a class variable. Average weight gains of the kits between days 3 and 8, and days 8 and 13 were calculated and subjected to analysis of variance to test the effects of litter size, bromocriptine treatment and their interaction, and expressed as mean ± standard error. Doe weights were treated the same way, i.e. average weight gains were calculated and subjected to the same analyses as the kit weight gains.

The proportions of kit deaths per litter on days 8 and 13 were analysed using the SAS procedure for categorical data modelling (logit-transformation). Differences between group means were tested according to pre-planned comparisons using the Chi-Square statistic. Data were analysed using the computer statistical package SAS (1985).

RESULTS

There were significant treatment effects on day 8 ($P<0.05$) and day 13 ($P<0.001$) on the proportion of kit deaths (Table 2). On both of these days, the medium and high dose rates (0.4 and 0.8 mg/kg/day) showed greater mortality in the kits than the control or low (0.2mg/kg/day) dose rates. By day 17 (3 days after the end of treatment) there was a clear dose-relationship between treatment and kit mortality, with highest kit mortality in the medium and high dose groups.

TABLE 2: Effect of treatment of NZ White rabbit does with CB154 (days 3-14 of lactation) on the proportion of kit deaths at selected days from kitting.

Treatment Group:	Proportion of Kit Deaths Day 8	Day 13	Day 17
Control	-3.18 ± 1.02^{a} (4)[2]	-1.39 ± 0.50^{ab} (20)	-1.39 ± 0.50^{a} (20)
Low	-2.30 ± 0.61^{a} (9)	-1.98 ± 0.53^{a} (12)	-0.31 ± 0.35^{ab} (42)
Medium	-0.14 ± 0.38^{b} (46)	0.59 ± 0.39^{c} (64)	0.59 ± 0.39^{bc} (64)
High	-0.51 ± 0.42^{b} (37)	-0.51 ± 0.42^{bc} (37)	0.89 ± 0.71^{c} (71)

[1] Logit-transformed.

[2] Back-transformed (%).

[abc] Means within days having superscripts with letters in common are not significantly different ($P>0.05$)

$$\text{proportion} = \frac{\text{number of dead kits/litter}}{\text{total number of kits/litter}} \times 100$$

There were no significant interactions between litter-size group and treatment in any of the models tested. Although kit weight gain from day 3 to day 8 of life was inversely proportional to dose, differences between treatment groups were not significant over this interval (Table 3). Kit weight gain from day 8 to day 13 of life was significantly ($P<0.01$) affected by treatment, with the control group exhibiting the highest weight gain, followed by the medium and low groups. The high group kits actually lost weight over that period.

Treatment with bromocriptine significantly affected the live weight change of the does during the period day 3 to day 8 of lactation ($P<0.05$) (Table 3). The control does lost weight, while the groups treated with CB154 all gained weight. There were insufficient observations per group to analyse the second growth period in the does, because only does with kits still alive were re-weighed at day 13 of lactation.

TABLE 3: Effect of CB154 treatment on kit and doe 5-day weight gain.

Treatment Group:	Kit Weight Gain (g) (surviving kits) day 3-8	day 8-13	Doe Weight Gain (g) day 3-8
Control	64.2 ± 17.0^{a} (24)[1]	83.7 ± 11.4^{a} (20)	-62.9 ± 68.5^{a}
Low	57.7 ± 17.0^{a} (30)	18.7 ± 11.4^{b} (29)	311.8 ± 61.6^{b}
Medium	30.5 ± 25.3^{a} (15)	33.5 ± 17.2^{b} (10)	281.4 ± 91.6^{b}
High	21.7 ± 17.0^{a} (15)	-0.8 ± 14.9^{b} (11)	210.5 ± 68.5^{b}

[1] number of kits surviving on the last day of the period

[ab] means within days having superscripts with letters in common are not significantly different ($P>0.05$)

DISCUSSION

The highest dose rate (0.8 mg/kg/day) used in this trial was chosen to give a range of doses greater than that reported previously in rabbits. Injecting rabbits with approximately 0.3 mg/kg/day starting on day 7 of lactation caused the death of all kits (Taylor and Peaker 1975), whereas a similar dose given later in lactation (from day

14) had no effect on kit mortality (Fortun *et al.* 1994). The results of our trial suggest that lactating does are more resistant to CB154 than previously reported (Taylor and Peaker 1975).

CB154 treatment of the does increased kit mortality, the upper limit on day 17 being achieved by the medium dose. Complete mortality did not occur, even at the highest dose. CB154 successfully retarded the weight gains of the surviving kits, with the upper limit of effect on weight gain being at the highest dose. Average weight gains of the control group kits over day 3 to day 8 (64g) and day 8 to day 13 (84g) of doe lactation compare favourably with those reported in kits of the same breed (52g and 20g, respectively) (Oetting *et al.* 1989), suggesting that the control animals grew "normally".

The does in the control group lost weight (63g) between day 3 and day 8 of lactation. A weight loss in lactating does was also found by Fortun *et al.* (1993), who suggested that this could be due to mobilisation of maternal body protein and lipid reserves as increased intake alone was not sufficient to maintain lactation. In contrast, does in the treatment groups gained weight during this period, presumably because of reduced milk yield, as indicated by lower growth of kits. A maternal weight gain in treated does was also found by Fortun *et al.* (1994).

In summary, while CB154 treatment was effective in reducing kit growth and survival, consistent with reducing milk supply in their dams, our results suggest that does are more resistant to the effects of this drug than reported previously (Taylor and Peaker 1975). Given that a higher oral dose would be required to achieve the effects of systemic treatment at the doses used here, this raises doubts about the practicalities of using CB154 in baits.

REFERENCES

Buys, N.; Vanmontfort, D.; Peeters, R.; van Isterdael, J.; Decuypere, E.; Kuhn, E.R. 1995. Bromocriptine is effective in reducing milk production in ewes during lactation, but has no additional effect during drying off. *Animal Science* **60:**203-208

Cingotti, M.; Magnin, G. 1986. Comparative efficacy of cyclofenil and bromocriptine in inhibition of lactation. *Revue Francaise de Gynecologie et d'Obstetrique* **81(6-7):**369-372

Cowie, A.T.; Hartmann, P.E.; Turvey, A. 1969. The maintenance of lactation in the rabbit after hypophysectomy. *Journal of Endocrinology* **43:**651-662

Falconer, I.R.; Fiddler, T.J. 1970. Effects of intraductal administration of prolactin, actinomycin D and cycloheximide on lipoprotein lipase activity in the mammary glands of pseudopregnant rabbits. *Biochimica et Biophysica Acta* **218:**508-514

Fortun, L.; Prunier, A.; Lebas, F. 1993. Effects of lactation on fetal survival and development in rabbit does mated shortly after parturition. *Journal of Animal Science* **71:**1882-1886

Fortun, L.; Bolet, G.; Lebas, F. 1994. Influence of prolactin on foetal survival in rabbit does. *Animal Reproduction Science* **37:**75-84

Oetting, B.C.; Rakes, J.M.; Johnson, Z.B. 1989. Growth rate and body measurements in New Zealand white, Japanese white and cross-bred rabbits. *Journal of Applied Rabbit Research* **12(2):**116-122

Okkens, A.C.; Bevers, M.M.; Dieleman, S.J.; Willemse, A.H. 1990. Evidence for prolactin as the main luteotrophic factor in the cyclic dog. *The Veterinary Quarterly* **12(4):**193-201

RBAG. 1996. Rabbits at a glance. Rabbit Biocontrol Advisory Group.

SAS. 1985. SAS Users Guide, Version 5. Cary, NC, U.S.A., SAS Institute Inc.

Taylor, J.C.; Peaker, M. 1975. Effects of bromocriptine on milk secretion in the rabbit. *Journal of Endocrinology* **67:**313-314