Luteolytic potency of a prostaglandin analogue at different stages of the oestrous cycle in red deer (*Cervus elaphus*) hinds

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The luteolytic effect of the prostaglandin $F_{2\alpha}$ analogue, cloprostenol, was investigated in red deer by monitoring concentrations of plasma progesterone, the induction of oestrus and ovulation, and fertility. Oestrus was synchronized in 48 adult hinds by intravaginal delivery of exogenous progesterone for 12 days and i.m. injection of 250 iu pregnant mares' serum gonadotrophin at progesterone withdrawal. A single i.m. dose of 500 μ g cloprostenol was administered at day 4, 6, 8, 10, 12, 14 or 16 of the subsequent oestrous cycle ($n = 6$ hinds per treatment; day 0 = oestrus). Six other hinds were monitored by intensive collection of blood samples between day 16 and day 19 to define changes in plasma progesterone concentrations during spontaneous luteolysis. Samples of jugular blood, collected every second day throughout the study and every 6 h for 78 h from the time of administration of cloprostenol, were analysed for plasma concentrations of progesterone and LH. Oestrus was detected by continuous observation during the period of intensive collection of blood samples and all hinds were subjected to transrectal ultrasonography to assess pregnancy status. On the basis of changes in plasma progesterone concentrations, cloprostenol induced complete luteolysis in all hinds treated on days 8–16 and in five of six hinds treated on day 6. Oestrus, ovulation and conception occurred in 25 (69%), 28 (78%) and 25 (69%), respectively, of hinds treated on days 6–16 inclusive ($n = 36$). Luteolysis was incomplete in all hinds treated on day 4, and none of the animals exhibited oestrus or ovulated; luteolysis was incomplete for one hind treated on day 6. Short luteal cycles (< 12 days duration) occurred in six hinds following cloprostenol treatment, but this occurred only in hinds treated on day 6 ($n = 3$), day 8 ($n = 1$) or day 10 ($n = 2$). The mean intervals from injection of cloprostenol to onset of oestrus and peak preovulatory LH surge values were significantly shorter for hinds treated on day 6 or day 8 (~ 50 h and 52 h for oestrus and LH surges, respectively) than for those treated on days 10–16 inclusive (60 h and 65 h, respectively) ($P < 0.05$). It is concluded that on day 4 of the cycle, the cervine corpus luteum is refractory to a single injection of the prostaglandin analogue, whereas on day 6 the corpus luteum is responsive in most animals, and that whereas corpora lutea at days 8–10 are responsive in all animals, a high incidence of subsequent premature luteal regression may occur. Fertility to cloprostenol-induced oestrus and ovulation following natural mating was high, especially for hinds treated on days 12, 14 and 16 of the oestrous cycle (i.e., $> 80\%$ conception rate).

Introduction

The cervid oestrous cycle has many similarities to that of other ruminants, exhibiting distinct follicular, luteotrophic and luteolytic phases (Asher and Fisher, 1991). There is considerable evidence implicating uterine secretion of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) in the regression of the corpus luteum of the oestrous cycle in many species (Knickerbocker *et al.*, 1988). Studies have

shown that spontaneous luteolysis in fallow deer (*Dama dama*) is associated with episodic release of uterine $PGF_{2\alpha}$ between day 16 and day 20 of the oestrous cycle (Asher *et al.*, 1988). Characteristically, luteolysis involves a rapid decline in peripheral plasma progesterone concentrations, and oestrus and ovulation usually occur within 48–96 h (McCracken *et al.*, 1970; Louis *et al.*, 1974). The development of potent synthetic analogues of $PGF_{2\alpha}$ has enabled synchronization of oestrus to be performed in many domestic species by premature induction of luteal regression. Administration of prostaglandin analogues

Received 25 August 1994.

during the oestrous cycle induces luteolysis in a number of cervids including fallow deer (Asher and Thompson, 1989; Asher *et al.*, 1990; Jabbour *et al.*, 1993), red deer (*Cervus elaphus scoticus*; Asher *et al.*, 1992; Fisher *et al.*, 1994) and North American wapiti (*Cervus elaphus nelsoni*; Glover, 1985). However, efficacy of induction of luteolysis at different stages of the oestrous cycle is poorly defined for cervids. Studies in sheep, goats and cattle have shown that corpora lutea are refractory to the luteolytic influences of prostaglandin analogues before days 3–5 of the oestrous cycle (Rowson *et al.*, 1972; Hearnshaw *et al.*, 1974; Roche, 1974; Acritopoulou and Haresign, 1980). Preliminary studies on red deer and North American wapiti indicated that refractoriness may persist for longer in cervids, and corpora lutea at day 11 and day 9 can exhibit marked refractoriness in the two subspecies, respectively (Glover, 1985; Fisher *et al.*, 1994).

The objective of the present study was to evaluate the efficacy of a prostaglandin analogue in inducing luteolysis in farmed red deer throughout the oestrous cycle, by assessing changes in progesterone secretion, the occurrence of oestrus and ovulation, and the level of fertility following oestrus induced by a single injection of cloprostenol, a synthetic prostaglandin. We also sought to define changes in progesterone secretion during spontaneous luteolysis by monitoring untreated hinds between day 16 and day 19 of a synchronized oestrous cycle.

Materials and Methods

Animals and management

A total of 48 mature (3–10 years old) red deer hinds at the Ruakura Agricultural Centre (37°46'S, 175°20'E) were run in the continuous presence of one or more vasectomized stags from calf removal on 16 March until administration of prostaglandin analogue on 21 April. Thereafter, they were run with one or more fertile stags until 30 May. They were grazed on ryegrass–white clover pastures and offered supplements of meadow hay. Water was provided *ad libitum*.

Experimental protocol

Hinds were allocated, on the basis of livemass, to eight treatments ($n = 6$ hinds per treatment with treatment average livemass of 96–97 kg). Oestrus of hinds was synchronized by intravaginal placement of a single CIDR (controlled internal drug releasing) device (CIDR-type G, 0.3 g progesterone per device; Agricultural Division, CHH Plastic Products Group Ltd, Hamilton) to each hind for 12 days, and the CIDR device was replaced on day 8. An i.m. injection of 250 iu pregnant mares' serum gonadotrophin (PMSG; Folligon; Intervet, Lane Cove, NSW) was administered at the time of removal of the second device to ensure successful induction of oestrus and ovulation (Fennessy *et al.*, 1991). The regimen for synchronization of oestrus was staggered by intervals of 2 days between successive treatment groups to produce a range of subsequent luteal ages (4–16 days) on 21 April, at which time 500 µg cloprostenol (2.0 ml Estrumate; Imperial Chemical Industries PLC, Wilmslow, Cheshire) was administered by i.m. injection to all

but one group of hinds. Luteal ages at time of injection, defined as the interval from the synchronized oestrus (predicted to occur at around 48 h after removal of CIDR devices; Asher *et al.*, 1992), were 4, 6, 8, 10, 12, 14 and 16 days. The remaining six hinds were synchronized with the last group and were at day 16 at the start of the intensive monitoring period.

Collection of blood samples

Blood samples were collected from all hinds by jugular venepuncture every second day from 20 March to 27 May. Additional jugular samples were collected every 6 h for 78 h from the time of administration of cloprostenol. The plasma samples were assayed for progesterone to assess changes in luteal status, and for LH to determine the incidence and time of onset of the preovulatory LH surge.

Behavioural observations

During the period of intensive collection of blood samples (21–24 April), observations to detect oestrus and mating were conducted continuously from an enclosed observation platform fitted with halogen floodlights. Identification of individual animals was possible using a monocular telescope ($\times 20$). The hinds were run with single fertile stags during this period, and stags were replaced every 24 h.

Pregnancy determination

Rectal ultrasonography (White *et al.*, 1989; Wilson and Bingham, 1990) was performed 33 and 43 days after administration of cloprostenol to determine pregnancy status.

Hormone assays

Plasma concentrations of progesterone were determined in duplicate by the direct radioimmunoassay validated previously for red deer plasma (Asher *et al.*, 1992). All samples from each hind were included within a single assay. Samples with low, medium and high concentrations of progesterone were included as control samples at frequent intervals in each assay. The interassay coefficients of variation were 17.6% for the low control (mean 0.45 ng ml^{-1}), 12.1% for the medium control (4.83 ng ml^{-1}) and 10.0% for the high control (9.90 ng ml^{-1}) samples, respectively. The intra-assay coefficients of variation were 14.3%, 8.9% and 6.7% for the three control samples, respectively. Sensitivity of the standard curve, defined as the first point that was significantly different from 0, was 0.10 ng ml^{-1} .

Plasma LH concentrations were determined in duplicate by the heterologous radioimmunoassay described for sheep plasma by Scaramuzzi *et al.* (1970) and validated for red deer plasma by Kelly *et al.* (1982) and Asher *et al.* (1992). The sheep pituitary LH preparation used for standards and iodinated tracer was NIH-LH-S₁₁. The LH antibody, which was raised in a rabbit, also using NIH-LH-S₁₁ as the antigen, was used in the assay at a final dilution of 1:200 000. Crossreactivities with other proteins were described by Kelly *et al.* (1982). All samples from each hind were included within

Table 1. Incidence of oestrus, a preovulatory LH surge, conception and short luteal cycles, and mean ($\pm$ SEM) times from cloprostenol treatment to the onset of oestrus and the LH peak for nonpregnant red deer hinds treated at various stages of the oestrous cycle

Treatment	Number of hinds	Number of hinds exhibiting oestrus	Mean time (h $\pm$ SEM) to onset of oestrus	Number of hinds ovulating (LH surge)	Mean time (h $\pm$ SEM) to LH peak	Number of hinds conceiving after induced oestrus	Number of hinds exhibiting short luteal phase at the cycle following cloprostenol administration
Day 4	6	0	—	0	—	0	0
Day 6	6	4	50.5 $\pm$ 2.2	5	55.2 $\pm$ 1.2	3	3
Day 8	6	3	48.2 $\pm$ 4.8	4	46.5 $\pm$ 6.7	4	1
Day 10	6	4	59.3 $\pm$ 3.8	4	61.5 $\pm$ 4.5	4	2
Day 12	6	4	60.8 $\pm$ 2.6	4	64.5 $\pm$ 2.9	4	0
Day 14	6	5	60.6 $\pm$ 3.6	6	65.0 $\pm$ 3.6	5	0
Day 16	6	4	62.0 $\pm$ 6.4	5	66.0 $\pm$ 5.0	5	0
Untreated hinds*	6	1	—	2	—	—	—
Total	48	25	57.4 $\pm$ 1.8	30	60.2 $\pm$ 2.0	25	6

*Day 16 at the start of intensive collection of blood samples.

a single assay. The interassay and intra-assay coefficients of variation for multiple determination of a cervine control sample (mean 5.40 ng ml⁻¹) were 9.7% and 4.8%, respectively, and the sensitivity of the standard curve was 0.03 ng NIH-LH-S₁₁ (0.30 ng ml⁻¹). The upper limit of the assay was 15 ng ml⁻¹, but samples exceeding this value were not reassayed following dilution as we required data on the incidence, rather than characteristics, of the preovulatory LH surge (after Asher *et al.*, 1992).

Statistical analyses

Data on the intervals from treatment to the onset of oestrus and the LH surge, and plasma progesterone concentrations following administration of cloprostenol were analysed with respect to treatment day by analysis of variance (GENSTAT V; Lawes Agricultural Trust, Rothamsted Experimental Station). Means are presented with either the standard error of the mean (SEM) or standard error of difference (SED) based on pooled variance.

Results

Oestrous and ovulatory responses

Oestrus was observed for 24 of 42 (57%) hinds within 78 h following administration of cloprostenol, and for 1 of 6 untreated hinds during the same observation period. The incidence of oestrus varied between treatments (Table 1), and no hinds treated on day 4, and between 3 and 5 animals in other treatment groups (days 6–16), exhibited oestrus. A preovulatory LH surge (i.e. values > 10 ng ml⁻¹) was observed within the same monitoring period for 28 of 42 (67%) treated hinds and 2 of 6 (33%) untreated hinds. A preovulatory LH surge was recorded in all hinds that exhibited oestrus. The

incidence of surges again varied between treatments (Table 1), and no hinds treated on day 4, and between 4 and 6 hinds in other treatment groups, exhibited a preovulatory LH surge. Mean ($\pm$ SEM) intervals from injection of cloprostenol to oestrus and the LH peak were 57.4 $\pm$ 1.8 h and 60.2 $\pm$ 2.0 h, respectively. However, there was a significant effect of day of treatment, with oestrus/ovulatory hinds treated on day 6 or day 8 exhibiting shorter intervals than those treated on days 10–16 ($P < 0.05$; Table 1). A total of 25 treated hinds conceived following mating at the induced oestrus/ovulation, representing between 3 and 5 pregnancies for hinds treated on days 6–16, inclusive, and none for hinds treated on day 4 or untreated hinds (Table 1). Analysis of profiles of plasma concentrations of progesterone for individual hinds indicates that six hinds exhibited short luteal cycles (i.e. < 12 days duration) following injection of cloprostenol, and the incidence of short cycles was restricted to hinds treated on day 6 ($n = 3$), day 8 ($n = 1$) or day 10 ($n = 2$) (Table 1).

Profiles of plasma progesterone concentrations

Mean plasma concentrations of progesterone at the time of administration of cloprostenol (time 0) varied between treatments according to stage of luteal development, being between 2 and 3 ng ml⁻¹ for days 4–8, inclusive, and 3.5 and 5.5 ng ml⁻¹ for days 10–16 (Fig. 1). Administration of cloprostenol caused a rapid decline (i.e. > 50% reduction within 6 h) in mean progesterone concentrations in all groups. However, all hinds treated on day 4 exhibited an apparent luteal recovery within the monitoring period, manifest as a progressive increase in mean concentrations after 36 h, with values exceeding those of time 0 by 78 h. Hinds in all other groups exhibited decreasing concentrations of progesterone throughout the monitoring period, and mean concentrations for each group remained below 1 ng ml⁻¹ from 18 h after injection. The exception to this was one

Fig. 1. Profiles of mean plasma concentrations of progesterone for red deer hinds treated with 500 µg cloprostenol on days 4 (●), 6 (○), 8 (■), 10 (□), 12 (▲), 14 (△) or 16 (◇) of the oestrous cycle. Each profile represents the mean of six animals blood sampled every 6 h for 78 h. Vertical bars represent SED.

hind treated on day 6, which failed to exhibit oestrus or an LH surge and showed evidence of luteal recovery within 30 h of treatment (Fig. 2). Mean progesterone concentrations for hinds treated on day 4 were significantly higher than those of all other groups from 54 h after injection ($P < 0.05$; Fig. 1).

Recovery of luteal progesterone secretion within 78 h of injection of cloprostenol was evident for hinds treated on

day 4, and a continued increase of mean values occurred over the next 8–10 days, followed by spontaneous luteolysis between 4 and 6 May (17–19 days from day 0) (Fig. 3). By contrast, luteolysis following injection of cloprostenol was demonstrably complete within 78 h for hinds treated on day 14, and 5 of 6 hinds conceived at the induced oestrus and exhibited increasing luteal progesterone secretion between 25 April and 3 May. Thereafter, mean plasma

Fig. 2. Profiles of plasma concentrations of progesterone for red deer hinds treated with 500 µg cloprostenol on day 6 of the oestrous cycle, showing the mean ($\pm$ SEM) concentrations for five hinds that exhibited oestrus or an LH surge, showing full luteal regression (●) and the individual profile for one hind that failed to exhibit either oestrus or an LH surge, and in which luteal regression did not occur (○).

concentrations of progesterone fluctuated between 2 and 6 ng ml⁻¹ (Fig. 3).

Spontaneous luteolysis

Untreated hinds were predicted to be at day 16 of the oestrous cycle at the start of the 78 h intensive blood sampling regimen (that is, time 0). Five of these hinds exhibited spontaneous luteolysis during the monitoring period (days 16–19), and the mean concentrations of plasma progesterone declined progressively from 3.5 ng ml⁻¹ (time 0) to 0.3 ng ml⁻¹ by 60 h (Fig. 4). The hind that failed to exhibit luteolysis during this period displayed high concentrations of plasma progesterone (2.9–4.7 ng ml⁻¹) throughout the monitoring period (Fig. 4), but appeared to have undergone complete luteolysis 48 h later (25 April).

Discussion

The study reported here indicates that, for red deer, the corpus luteum is refractory to the luteolytic action of a single injection of 500 µg cloprostenol when administered on day 4, largely responsive on day 6 and fully responsive by day 8 after oestrus, as evidenced by changes in plasma concentrations of progesterone. Hinds treated on day 4 exhibited an initial decline in progesterone secretion over the 24 h after cloprostenol delivery. However, there was an apparent rebound in luteal activity as progesterone concentrations were restored to pretreatment values and most hinds failed to exhibit oestrus. In contrast, most hinds (5 of 6) treated on day 6 and all hinds treated on days 8–16 underwent complete luteolysis, and plasma progesterone concentrations remained below

0.5 ng ml⁻¹ from 48 to 78 h after cloprostenol delivery. Furthermore, most of these hinds were observed in oestrus or exhibited a preovulatory LH surge within 78 h. In these respects, the responsiveness of red deer hinds to exogenous prostaglandins in this study was similar to that observed for sheep (Acritopoulou and Haresign, 1980), goats (Hearnshaw *et al.*, 1974) and cattle (Rowson *et al.*, 1972; Roche, 1974); all of these species tended to exhibit full luteolytic responses if treated on or after day 5 of the oestrous cycle.

It should be noted that the data from the present study conflict with earlier studies on red deer (Fisher *et al.*, 1994) and North American wapiti (Glover, 1985), both of which demonstrated a marked degree of refractoriness to a prostaglandin analogue when administered on days 9–11 of the oestrous cycle of monovulating females. The different luteolytic responses of hinds in the two red deer studies (Fisher *et al.*, 1994; present study) are most likely the result of subtle variations in luteotrophic support of the corpus luteum reflecting differences between regions (the two studies were conducted 1000 km latitude apart) and years. Although initial synchronization treatments were conducted at similar times of the year (late March–early April), subtle differences in timing relative to spontaneous reproductive activity (i.e. the rut) between years and regions may have occurred, resulting in differences in hypothalamic–pituitary support of the corpora lutea. Macmillan *et al.* (1985a, b) and Henderson and McNatty (1977) reported that pituitary support of the corpus luteum in other species determines the sensitivity of luteal tissue to the luteolytic effects of endogenous or exogenous prostaglandin. It would be reasonable to assume that reduced luteotrophic support renders cervine corpora lutea more sensitive to the luteolytic effects of prostaglandins. The issue of refractoriness in red deer requires further clarification if prostaglandins are to be used for induction of luteolysis without reference to stage of the oestrous cycle.

The intervals from the time of administration of cloprostenol to the onset of oestrus and the preovulatory LH surge were shorter for hinds treated on day 6 and day 8 than for hinds treated later in the oestrous cycle. This probably arises from a more rapid reduction in progesterone secretion to basal concentrations as a consequence of lower initial luteal activity at the time of injection. A similar phenomenon is apparent from the data of Acritopoulou and Haresign (1980) for sheep, although overall the intervals at all stages of the oestrous cycle were shorter for sheep than for red deer (e.g. 37 h versus 57 h to onset of oestrus). Similarly, the interval from cloprostenol injection to onset of oestrus for fallow deer treated on day 13 of their oestrous cycle was shorter (i.e. 48 h) than that observed for red deer (Asher and Thompson, 1989). Reasons for variation between species remain to be resolved.

The occurrence of short luteal cycles in some hinds following cloprostenol treatment on days 6–10 is similar to the phenomenon observed following administration of prostaglandin to sheep (Schiewe *et al.*, 1990). Premature luteal regression was restricted to hinds treated early in the oestrous cycle, supporting the suggestion that transient corpora lutea are a result of insufficient duration of progesterone priming before the induction of luteolysis. As a consequence of the incidence of short luteal cycles in red deer hinds, fewer individuals treated between day 6 and day 10 are likely to

Fig. 3. Longitudinal profiles of mean ($\pm$ SEM) plasma concentrations of progesterone for red deer hinds treated with 500 μ g cloprostenol on (a) day 4 and (b) day 14 of the oestrous cycle. Mean values for blood samples collected at intervals of 6 h for 78 h from cloprostenol injection on 21 April are represented by solid symbols. The shaded bar represents the period of treatment with intravaginal controlled internal drug releasing (CIDR) devices.

conceive as a result of induced oestrus and ovulation than those treated after delivery of prostaglandins later in the cycle. This was the case in the present study. On the basis of this observation, and given the apparent complete refractoriness to prostaglandins on day 4, it would seem that effective practical use of exogenous prostaglandins to induce fertile oestrus and ovulation in red deer hinds should be confined to later stages of the oestrous cycle (i.e. days 12–16). This finding supports earlier suggestions that application in red deer without reference to known stages of the oestrous cycle necessitates delivery of two injections of prostaglandins 10–12 days apart (Fennessy *et al.*, 1989).

In the study reported here, in which hinds were placed with two fertile stags immediately after delivery of cloprostenol, fertility was surprisingly high. In all, 25 of the 42 treated hinds became pregnant (60%). However, if one excludes hinds treated on day 4 (i.e. no oestrous and ovulatory response to treatment) and the six hinds that exhibited short luteal cycles in response

to treatment, 83% of remaining hinds conceived as a result of induced ovulation. Such high fertility (which approaches conception rates following natural mating to progesterone-synchronized oestrus; Fennessy *et al.*, 1991) was unexpected because of studies on fallow deer that demonstrated reduced fertility of does with cloprostenol-induced ovulation relative to those exposed to other forms of synchronization (Asher *et al.*, 1992; Jabbour *et al.*, 1993).

Spontaneous luteolysis occurred in five of six untreated hinds between day 16 and day 19, which is in accord with the known duration of the oestrous cycle (18 days) for red deer (Guinness *et al.*, 1971; Adam *et al.*, 1985). In general, reductions in plasma concentrations of progesterone for these hinds proceeded at slower rates than for hinds receiving a single injection of cloprostenol, with indications for some hinds that spontaneous luteolysis may have been initiated before the start of intensive collection of blood samples on day 16. Only one untreated hind was observed in oestrus, and only two

Fig. 4. Profiles of mean ($\pm$ SEM) concentrations of plasma progesterone for six untreated red deer hinds during the oestrous cycle, including data for blood samples collected every second day from removal of CIDR devices ($\circ$) and every 6 h for 78 h from day 16 of the oestrous cycle (21 April) for five hinds exhibiting spontaneous luteolysis ($\bullet$) and one hind that failed to initiate luteolysis ($\blacktriangle$).

untreated hinds exhibited a preovulatory LH surge during the 78 h of intensive blood sampling, even though luteolysis appeared to be complete in most individuals by 60 h. This finding indicates a general lack of synchrony relative to treated hinds. With respect to the pattern of progesterone secretion, spontaneous luteolysis was similar to that observed in fallow deer (Asher *et al.*, 1988).

In summary, the luteolytic response to the prostaglandin analogue in red deer from about day 6 of the oestrous cycle is in accord with that reported for other ruminant species but conflicts with other studies in red deer, which have indicated refractoriness as late as days 9–11. Levels of synchronization and fertility observed in the study reported here indicate considerable potential for practical application of induced luteolysis for artificial breeding of red deer, and administration of cloprostenol between day 12 and day 16 was particularly promising.

The authors thank the staff of the Ruakura Deer Unit for their valued assistance during these studies.

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