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Potential Uses of Prostaglandins (PGF2a) for the Practitioner and Cattle Industry

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Prostaglandins are potent biological compounds which affect many physiological mechanisms. They comprise a family of 20-carbon fatty acids which occur naturally in many body tissues. Prostaglandins, unlike circulating hormones, are thought to produce their biological activity by a direct local action, primarily by altering smooth muscle contractility and manipulating hormonal activity. Prostaglandins are rapidly metabolized by passage into areas of the body such as the lungs.

The compound which currectly is of greatest interest to reproductive physiologists is Prostaglandin F_{2a} (PGF_{2a}). This compound has the ability to cause rapid regression of the corpus luteum. Many researchers believe that prostaglandins are the uterine luteolytic factor produced near the end of the estrous cycle, which are responsible for rapidly terminating the functional life of the corpus luteum and controlling the onset of estrus and ovulation.

The objective of this paper is to review recent reproductive research dealing with PGF_{2a} in cattle and to outline potential uses for the veterinarian and cattle industry, pending approval for commercial use by the Food and Drug Administration (FDA). PGF_{2a} is currently available for use in non-lactating cows on a controlled experimental basis in order to establish data on dosage, safety and efficacy.

Review of PGF_{2a} Reproductive Research in Cattle

Prostaglandins (PGF_{2a}) were deposited into the lumen of the uterine horn of cycling cows to determine the effects on the corpus luteum (6). Six cows were treated with 5 mg. PGF_{2a} in the uterine horn ipsilateral to the corpus luteum on days 7, 11 and 15 of the estrous cycle (estrus = day 0) and on day 11 of the estrous cycle five cows were treated with 5 mg. PGF_{2a} in the uterine horn contralateral to the corpus luteum. These cows were palpated per rectum at 12-hour intervals to detect ovarian changes. Blood was collected from jugular cannulae to monitor peripheral levels of progesterone, luteinizing hormone (LH) and estradiol. During the first 24 hours following treatment, the diameter of the corpus luteum decreased from 2.5 to 1.6 cm.

Table 1

Changes in Corpus Luteum Size and in Blood Serum Progesterone and estradiol after PGF_{2a} in cows (6)

Interval after PGF_{2a}	Corpus luteum diameter	Blood serum progesterone	Blood serum estradiol
(hr)	(cm)	(ng/ml)	(pg/ml)
0	2.5 ± .1	3.6 ± .3	5.0 ± 1.0
12	--	1.7 ± .2	6.1 ± .4
24	1.6 ± .1	1.2 ± .2	11.3 ± .7
48	0.9 ± .2	1.0 ± .1	12.7 ± 1.3
72	< 0.9	0.8 ± .1	15.5 ± 1.7

(Table 1), while the level of progesterone declined from 3.6 to 1.2 ng./ml. There was a simultaneous increase in blood estradiol from 5.0 to 11.3 pg./ml. The diameter of corpus luteum was less than 1 cm. at the onset of estrus 72 hours after PGF_{2a} treatment while the level of progesterone had declined to only 0.8 ng./ml. and estradiol levels had tripled to 15.5 pg./ml. These values are consistent with those observed during the three days before estrus in untreated cows (9). These results support the idea that PGF_{2a} is a powerful luteolytic agent in cattle. The mean hourly intervals to peak luteinizing hormone levels (LH),

Table 2

Intervals to Peak LH, Onset of Estrus, and Ovulation after 5 mg. PGF_{2a} in Cattle (6)

PGF_{2a} Treatment Uterine Horn	Day of Cycle	Interval from PGF_{2a} to: Peak LH	Onset Estrus	Ovul-ation	Duration of Cycle after PGF_{2a}
		----(hours)----			(days)
Ipsilateral (6)	7	69	71	86	21.5
	11	68	68	94	20.8
	15	72	70	97	20.6
Contralateral (5)	11	77	76	100	
	average	71	72	95	21.0

the onset of estrus and ovulation were 71, 72 and 95 respectively (Table 2). The 23 hour interval from the onset of estrus to ovulation is considered normal for the cow. The results of this study were not affected by the stage of the estrous cycle selected for treatment or by the location of PGF_{2a} deposition in relation to the corpus luteum. The estrous cycles subsequent to treatment were all normal, indicating that the PGF_{2a} did not have a residual effect.

Although no problems were encountered in the intrauterine administration of PGF_{2a} during the luteal phase of the estrous cycle in this study, the uterus is very susceptible to infection at this time. As a result, a study was conducted to determine the effect of PGF_{2a} after intramuscular and intravaginal administration to heifers in the luteal phase of the estrous cycle. Thirty mg. of PGF_{2a} was injected into each of six diestrus heifers and

Table 3

Intervals to Peak LH, Onset of Estrus, and Ovulation after PGF_{2a} in 5 Heifers (5)

Interval	30 mg. Intramuscular	30 mg. Intravaginal
	----(hours)----	
Peak LH	64	128
Onset Estrus	74	117
Ovulation	104	138

was deposited in the anterior vagina near the cervix in an additional six diestrus heifers.

The results of the 30 mg. PGF_{2a} intramuscular treatment (Table 3) were comparable to the 5 mg. intrauterine deposition in the previous study. The interval to estrus after intravaginal administration was variable with a mean interval of 117 hours. Since the primary goal was to predict the time of ovulation, the results of the vaginal method of administration were too variable to permit the accurate prediction of the best time for insemination.

In the same heifer trial, 30 mg. of PGF_{2a} was injected intramuscularly into six heifers on day three of the estrous cycle before the corpus luteum was completely developed. The PGF_{2a} has no luteolytic effect on the estrous cycle in these heifers with a developing corpus luteum. It was concluded from these experiments that systemic administration of PGF_{2a} to luteal phase cattle is as effective as uterine deposition; however, PGF_{2a} is luteolytic only after day five of the estrous cycle.

PGF_{2a} is capable of inducing abortion and parturition in cattle by causing luteal regression. Injections of 15 and 30 mg. PGF_{2a} produced abortions in three of six cows pregnant 40 to 120 days within 14 days after treatment, while 45 and 150 mg. caused abortions in all 20 cows also pregnant 40 to 120 days within two to seven days after treatment (Table 4). PGF_{2a} was less effective in inducing abortion after 120 but before 250 days of gestation. A majority of these cows conceived again by 30 days after the induced abortion. The results of this study indicate that PGF_{2a} is capable

Table 4

Effects of PGF_{2a} on Pregnancy from 40 to 120 Days in Cattle (2)

PGF_{2a} Treatment	No. Cows	Abortions	Interval
		(%)	(Days)
0	8	0	
15 mg.	6	50	< 14
30 mg.	6	50	< 14
45 mg.	20	100	2-7
150 mg.	20	100	2 7

Table 5

Effects of Prostaglandins (PGF_{2a}) on Induction of Parturition in Cattle (3)

PGF_{2a} Dose	No. of Cows	Day of Gestation Injected	Calved	PGF_{2a} Calving Interval
(mg)				
5	3	263	278	15
15-90	30	268	271	3

of effectively terminating pregnancy prior to 120 days in cattle.

PGF_{2a} is also effective in inducing parturition in cattle. When 30 cows were injected with 15 to 90 mg. PGF_{2a} at 268 days of gestation, they calved three days later (Table 5). Parturition was delayed for 15 days or nearly to term, when three cows were injected with 5 mg. PGF_{2a} at 263 days of gestation. This information indicated that 15 mg. of PGF_{2a} will effectively terminate pregnancy after 268 days of gestation. Additional study is essential to determine the optimal dosage and time for inducing abortion or parturition.

Since there is a demand for controlled ovulation and group breeding of cattle, the fertility of cows inseminated after treatment with PGF_{2a} was measured to determine if it was reduced as it is after synchronization of estrus with progestagens. A fertility trial was conducted using beef cows with palpable corpora lutea as follows: 1) 66 control cows were inseminated at 12 hours after onset of estrus; 2) 51 cows were treated with 30 mg. PGF_{2a} subcutaneously and inseminated 12 hours after onset of estrus; and 3) 60 cows were given 30 mg. PGF_{2a} and inseminated at 72 hours and at 90 hours after PGF_{2a} without regard to estrus. Pregnancy was determined by palpation *per rectum* 35 to 60 days after breeding with fertility results listed (Table 6). The conception rate of the two treated groups was equal to the controls. The calves born from treated and subsequent cycles were normal. These results indicate that ovulation control with PGF_{2a} will permit group artificial insemination in both beef and dairy herds, eliminating the need for estrous detection.

Table 6

Fertility in Cattle Following Injection of 30 mg. Prostaglandin F_{2a} (4)

Group	No. Cows	Fertility
		(%)
Control, AI Estrus (12 hrs.)	66	58
PGF_{2a} AI Estrus (12 hrs.)	51	57
PGF_{2a} AI (72 and 90 hrs.)	60	58

Potential Uses of PGF_{2a} in Cattle

The potential uses of prostaglandins in control of reproductive cycles of cattle and other domestic animals were recently reviewed (1). Some of the potential uses in cattle are as follows:

1. Induction of abortion or parturition. PGF_{2a}, a powerful luteolytic agent, is very effective in causing regression of the corpus luteum which is essential to maintain pregnancy in cattle. A 45 mg. dosage of PGF_{2a} was effective in inducing abortion in 2-7 days in cows 40 to 120 days pregnant, while a 15 mg. dosage effectively induced parturition within three days in cows of 268 days of gestation (2,3). This information indicates that PGF_{2a} is capable of inducing abortion or parturition. However, additional controlled dose response data collected at different stages of the gestation period is essential for rational use of PGF_{2a} in these conditions.

2. Treatment of clinical conditions. PGF_{2a} should be effective in treating clinical conditions which require the regression of the corpus luteum or other luteal tissue for recovery. Conditions such as pyometra and mummified fetus are maintained by a persistent corpus luteum of estrus (8). Luteal cysts are partially luteinized cystic follicles which persist for a prolonged period of time and are characterized by anestrus (8). PGF_{2a} should be effective in treating these three conditions by causing luteal regression, resulting in the onset of estrus which causes dilation of the cervix, contractions of the uterus and discharging of the purulent exudate or mummified fetus.

Cows with a silent or unobserved estrus characterized by a functional corpus luteum and a normal uterus are a common clinical condition today. The current treatment of choice is to predict the stage of the estrous cycle based primarily on the size and consistency of the corpus luteum (10). All of these cows with a functional corpus luteum between day 5 and 18 of the estrous cycle will respond to PGF_{2a} therapy by coming into estrus in approximately three days.

3. Controlled ovulation for ova transfer and group breeding. PGF_{2a} is currently being used in ova transfer work to effectively control estrus and ovulation in donor and receptor cows (7). Food and Drug Administration regulations and cost are limiting current widespread usage for this purpose; however, it is being used successfully for synchronizing donor cows.

The greatest potential benefit of PGF_{2a} to the livestock industry is group breeding by artificial insemination without the need for estrous detection. PGF_{2a} causes rapid luteolysis when given after day five of the estrous cycle with a relatively uniform interval between injection and estrus of approximately 72 hours. It is possible to examine all animals *per rectum* and select only those with a functional corpus luteum for PGF_{2a} treatment. These animals can then be serviced at 85 to 90 hours after treatment without the need for estrous detection. Breeding at 72 and 90 hours following treatment with PGF_{2a} to control ovulation in a limited number of animals with functional corpora lutea resulted in fertility comparable to controls (4). Another possible procedure which would eliminate the need for palpation *per rectum* would be to give a series of two PGF_{2a} injections at weekly intervals and breed at 85 to 90 hours after the second treatment. Additional controlled fertility trials must be conducted with large numbers of animals under different feeding, environment and management systems to determine the best methods for achieving the most economical conception results.

Conclusions

Prostaglandin F_{2a} is a potent luteolytic agent in cattle with a functional corpus luteum after day five of the estrous cycle. The intrauterine administration of 5 mg. PGF_{2a} after day five resulted in the fairly uniform onset of estrus in 72 hours and ovulation in 95 hours after treatment. The intravaginal or intramuscular administration of 30 mg. PGF_{2a} was also effective in initiating the onset of estrus and ovulation in cows with functional corpora lutea; however, the results of intravaginal administration were more variable than with the other two methods of administration. The cycles subsequent to treatment were all normal indicating that there were no residual effects from treatment.

PGF_{2a} permits the veterinarian to effectively manipulate the corpus luteum and control many reproductive conditions. Potential veterinary uses of the luteolytic properties of PGF_{2a} in cattle include induction of abortion from 40 to 120 days of gestation, induction of parturition near term, treatment of clinical conditions such as pyometra, mummified fetus, luteal cysts, and cows with a silent or unobserved estrus characterized by a functional corpus luteum and normal uterus. The greatest potential use for PGF_{2a} is in ovulation control which will facilitate ova transfer work and permit group breeding of large numbers of cattle by artificial insemination without the need for estrous detection.

PGF_{2a} is a naturally occurring substance in humans as well as cows and has already been approved for human use in other countries. Additional controlled dosage efficacy and safety data are required before PGF_{2a} will be approved for commercial veterinary use by the Food and Drug Administration. Bovine practitioners are excited about the prospects of using prostaglandins to enhance the efficiency of the cattle industry.

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