Some Potential Uses of Prostaglandins in Domestic Animals

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Although the term prostaglandin (PG) may appear to be new, a group of physiologically active substances extracted from ovine vesicular glands were named prostaglandins by Von Euler in 1935. Prostaglandins are derivatives of the hypothetical 20-carbon prostanoic acid. Depending on the chemical structure of the cyclopentane ring, the PG's are divided into four series–A, B, E, or F. Each series has different physiological and pharmacological properties. A summary of some known biological activities for A, E and F PG's is given in Table 1. In some cases, different PG's produce opposing biological responses, indicating the varied biological activities of the PG's.

Table 1
Biological Activity of Prostaglandins

System	Prostaglandin	Action
Cardiovascular	PGA, PGE, PGF	decrease blood pressure increase blood pressure
Urinary (kidney)	PGA, PGE, PGF_2	increase blood flow cause Na and H_2O diuresis
Gastrointestinal	PGE, PGE_2, PGA	decrease gastric secretion increase motility
Respiratory	PGE, PGE_2, PGF_2	bronchodilation bronchoconstriction
CNA and peripheral nerves	PGE, PGE_2	inhibit norepinephrine

For example, PG's of the A and E series reduce blood pressure while those of the F series increase blood pressure. The biological activity of prostaglandins has been reviewed more thoroughly by Hinman (1972) and Oesterling, et al., (1972).

One of the most exciting properties of PG's as far as veterinarians are concerned was the discovery of PG's luteolytic action. Pharris and Wyngarden (1969) were the first to demonstrate in rats that $PGF_{2\alpha}$ induced luteolysis. This observation provided a potential clue to the identity of the uterine luteolysin which represented a means of controlling the estrous cycle. Although there is considerable evidence indicating that $PGF_{2\alpha}$ is the uterine "luteolysin," the final proof has thus far eluded researchers. Since the report that $PGF_{2\alpha}$ was luteolytic in rats, many reports on the luteolytic properties in several species have been published. Perhaps the reports that $PGF_{2\alpha}$ was luteolytic in cows, ewes, and mares (reviewed by Hafs, et al., 1974, and Oxender, et al., 1974) were of the most interest to veterinarians in large animal medicine.

Prostaglandin $F_{2\alpha}$ in Cattle

If cows with functional corpora lutea (diestrus) are treated with $PGF_{2\alpha}$, there follow rapid decreases in corpus luteum size and serum progesterone concentrations. Serum progesterone decreased more than 50% within 12 hours after 5 mg of $PGF_{2\alpha}$ were injected in the uterus (Figure 1). This rapid decrease continued until basal progesterone concentrations were approached within 36 hours after PGF_2 treatment. Similarly, serum progesterone decreased to baseline concentrations following treatment of cows with $PGF_{2\alpha}$ (25 to 30 mg) intramuscularly (IM) or subcutaneously (SC). Although systemic treatment apparently requires three-to-five times more $PGF_{2\alpha}$ to cause luteolysis than that required by the uterine route, and, because administration by IM or SC routes is much easier than catheterizing the cervix of diestrous cows or heifers to place $PGF_{2\alpha}$ in the uterus, all of the recent research in our laboratory involved IM or SC routes of treatment.

Serum estradiol increases rapidly in cattle following $PGF_{2\alpha}$ treatment (Figure 1). Also, an ovulatory surge of LH occurs nearly coincidental with the onset of estrus, approximately 72 hours after $PGF_{2\alpha}$ treatment (Figure 1). Therefore, the changes in progesterone, estradiol and LH following $PGF_{2\alpha}$ are very similar to those during luteolysis in untreated cattle and ovulation occurred with reasonable synchrony 95 hours after $PGF_{2\alpha}$ treatment. The effect of $PGF_{2\alpha}$ treatments therefore tend to mimic the effects of the natural uterine "luteolysin." However, since $PGF_{2\alpha}$ is only luteolytic in cattle between days four and 17 following ovulation, $PGF_{2\alpha}$ will cause luteolysis in about 2/3 of a random group of cattle treated at one time. About 1/3 of the cattle in a herd will be near estrus (from two days before to four days after estrus) and, therefore, an injection of $PGF_{2\alpha}$ is not luteolytic

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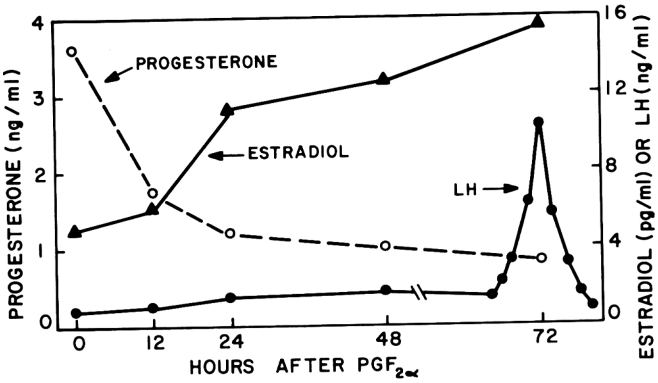

Figure 1. Blood progesterone, estradiol and LH after intrauterine PGF$_{2\alpha}$ (5 mg) in diestrus cows (Louis et al., J. Anim. Sci. 38:347, 1974).

in this group because they have no functional CL. But if a second treatment were given ten days later, these cows would then be on days seven to 14. The remaining ⅔ of the cows are initially between days 4 and 18 of the estrous cycle, and the first PGF$_{2\alpha}$ injection causes luteolysis in these cows and estrus three days later. The majority of these cows are on day seven of the estrous cycle ten days later. Therefore, theoretically, if a herd of cows were treated with PGF$_{2\alpha}$ twice 10 to 12 days apart, most of the herd could be synchronized by the second PGF$_{2\alpha}$ treatment. This two treatment regime appears to synchronize heifers and cows rather well as shown in Table 2. However, in some experiments, some of the cows and heifers were anestrus and PGF$_{2\alpha}$ treatment failed to synchronize these anestrous cows. The majority of the anestrous cattle in our experiments have been either beef cows nursing calves or heifers that are not sexually mature.

Breeding trials conducted in cows and heifers following PGF$_{2\alpha}$-induced luteolysis have indicated that fertility is normal in cattle inseminated during estrus following PGF$_{2\alpha}$ treatment. Also, when cattle were inseminated twice 80 to 95 hours after PGF$_{2\alpha}$ treatment without observation for estrus, fertility in

Table 2

Intervals From Injections of PGF$_{2\alpha}$ to Onset of Standing Estrus in Heifers and Suckled Cows

Number of Animals	Heifers First* PGF$_{2\alpha}$	Heifers Second* PGF$_{2\alpha}$	Cows Second* PGF$_{2\alpha}$
Total	59	59	66
Not observed in estrus	11	2	10
In estrus on day 1-2	10	0	0
3	19	25	32
4	15	15	9
5	3	6	2
6	0	6	2
7-11	1	5	11

*The two IM injections of PGF$_{2\alpha}$ were given 12 days apart.
Data from Hafs et al., Vet. Rec. 196:134, 1975.

treated groups equalled that in controls. Fertility in heifers inseminated once 80 hours after PGF$_{2\alpha}$ treatment appears to be equal to that in heifers inseminated twice. However, conception rates were slightly lower in cows nursing calves inseminated once at 80 hours after PGF$_{2\alpha}$ compared to cows inseminated twice following PGF$_{2\alpha}$ treatment, perhaps because of better synchrony of ovulation in heifers than cows following treatment (Hafs et al., 1974). The two major factors preventing higher pregnancy rates in cattle inseminated as a group following PGF$_{2\alpha}$ treatment are: 1) the variation in the length of time between PGF$_{2\alpha}$ treatment and ovulation and 2) the anestrous cows or heifers, particularly the postpartum anestrus in nursed cows.

In addition to luteolysis to synchronize ovulation, there are some therapeutic uses of PGF$_{2\alpha}$ that also may be important to veterinarians. 1) Cows one to three months postpartum with pyometra have been treated with PGF$_{2\alpha}$ (5 to 12.4 mg I.V.) causing the uterus to empty rapidly and these cows were in estrus three to four days after treatment as reported recently by veterinarians from Sweden. 2) Certainly, cows mated accidentally to the wrong bull or in other cases where an abortion is desirable, can be treated with PGF$_{2\alpha}$ (20 to 30 mg, I.M.) to produce an abortion. 3) Similar to corticoids, PGF$_{2\alpha}$ will induce parturition in cows during late gestation. Therefore, whenever clinical application of PGF$_{2\alpha}$ is considered, the possibility of pregnancy must be eliminated; if pregnant cows are treated, abortion or early parturition may result. In limited trials, a high incidence of retained placenta has been observed following PGF$_{2\alpha}$ induced parturition similar to that observed after corticoid-induced parturition. 4) Perhaps the most common reproductive problem treated by veterinarians is the cow reported to be in anestrus. When the ovaries are examined, a corpus luteum is frequently present, suggesting that failure to detect estrus was the cause of "anestrus." These "anestrous" cows could be efficiently treated with PGF$_{2\alpha}$, telling the herdsman to observe for estrus and inseminate these cows within about three to four days after PGF$_{2\alpha}$ treatment.

While the major biological action of PGF$_{2\alpha}$ studied in cattle to date has been related to the luteolytic properties, several other properties may be equally important. The pituitary hormones: growth hormone, prolactin, and adrenal corticotropin are released rapidly after PGF$_{2\alpha}$ treatment, increasing blood concentrations two to ten fold within one hour. These hormones are known to be related to growth and milk production, thereby suggesting a potential method for increasing production in cattle. These responses to PGF$_{2\alpha}$ are still in the laboratory testing stage of development.

Studies in our laboratory revealed that sperm transport and testosterone production are increased in PGF$_{2\alpha}$ treated bulls. At this time, we are not sure whether PGF$_{2\alpha}$ stimulates the Leydig cells directly to increase testosterone production or indirectly through pituitary gonadotropin release. Bulls injected with 40 mg $PGF_{2\alpha}$ one hour prior to semen collection ejaculated 20 to 40% more sperm than control bulls with or without sexual preparation, thereby suggesting that $PGF_{2\alpha}$ may be potentially valuable for use in AI bulls. The properties of $PGF_{2\alpha}$ that increase sperm transport in males do not eliminate the need for a sexual preparation period that is presently employed prior to semen collection because the increased sperm output from $PGF_{2\alpha}$ appeared to be additive with that from sexual preparation.

Prostaglandin $F_{2\alpha}$ in Other Large Animals

Although this paper has been prepared primarily for veterinarians engaged in bovine medicine, many veterinarians need to be informed about other species, especially horses, sheep and swine; therefore, we will briefly review some $PGF_{2\alpha}$ research in these species.

Several researchers have shown that $PGF_{2\alpha}$ causes luteolysis in mares and sheep similar to that described above in cows. When we injected (sc) mares with 15 mg $PGF_{2\alpha}$ seven to nine days after ovulation, progesterone decreased more than 50% within 12 hours (Figure 2). Progesterone continued to decrease and was below one ng/ml by 48 hours following $PGF_{2\alpha}$.

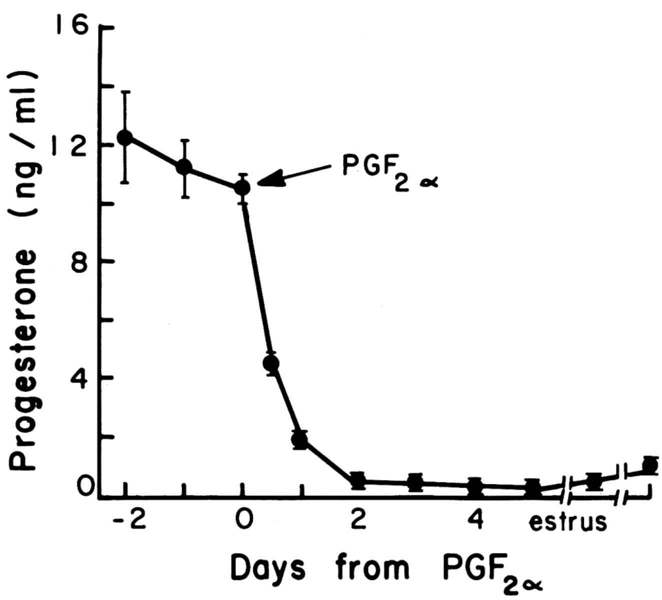

Figure 2. Blood progesterone in eight mares given $PGF_{2\alpha}$ (15 mg, sc) during diestrus.

All of the $PGF_{2\alpha}$-treated mares were in estrus within four days of treatment. Similar results have been reported by other research groups. $PGF_{2\alpha}$ treatment causes luteolysis in nearly all mares if given at least four days after ovulation (day 0), but it was not uniformly effective before day four. Estrus and ovulation in mares following $PGF_{2\alpha}$-induced luteolysis appears physiologically and endocrinologically normal. Fertility rates also appear to be normal; researchers at the University of Pennsylvania report a 65% conception rate in mares mated or inseminated following $PGF_{2\alpha}$ treatment.

$PGF_{2\alpha}$ also has been used to cause luteolysis in mares that have prolonged estrous cycles; these mares frequently may go 30 to 50 days between estrous periods. In addition to mares with prolonged estrous cycles, mares that have early embryonic losses frequently remain anestrus for long periods after the pregnancy has terminated, possibly due to pregnant mare serum gonadotropin (PMSG) secretion from the endometrial cups. However, Allen (University of Cambridge) has been successful in causing estrus with $PGF_{2\alpha}$ or an analog of $PGF_{2\alpha}$ in mares suffering early pregnancy losses.

Although the above discussion is brief, it does indicate potential uses of $PGF_{2\alpha}$ in mares. In addition to the uses of $PGF_{2\alpha}$ in mares and similar to observations described above for bulls, there has been one report indicating that stallions ejaculated more sperm following $PGF_{2\alpha}$ treatment than non-treated stallions.

Corpora lutea in ewes regress rapidly following $PGF_{2\alpha}$ treatment, indicating the luteolytic action of $PGF_{2\alpha}$ in sheep. Much of the earliest $PGF_{2\alpha}$ research was conducted in ewes and it appears that the luteolytic action of $PGF_{2\alpha}$ is similar in cows and ewes. And, as in cows, attempts to synchronize estrus and ovulation in ewes have centered on the problem with the 1/3 of the estrous cycle–near estrus and up to four days after ovulation–when PGF_2 is not luteolytic. Two successive treatments, eight to ten days apart, have been reasonably successful in synchronizing estrus and ovulation in ewes.

In sows, $PGF_{2\alpha}$ does not appear to be luteolytic unless they are given near the end of the luteal phase of the cycle, after day 12 following ovulation. Therefore, there seems to be little benefit in $PGF_{2\alpha}$ treatment of sows to produce luteolysis during the estrous cycle. However, other researchers have shown that $PGF_{2\alpha}$ can be used in sows to induce parturition during late gestation. It appears potentially possible to have sows farrow at a predetermined time by treating them with $PGF_{2\alpha}$. Studies are being

Table 3

Potential Uses of/for Prostaglandin $F_{2\alpha}$ in Animal Production

1. Luteolysis	estrous cycle control treat anestrus treat pyometra
2. Parturition or abortion	induce parturition treat prolonged gestation induce abortion prevent pregnancy from mismating
3. Sperm transport	increase ejaculated sperm
4. Androgen production	increase testosterone
5. Pituitary hormones	release growth hormone release prolactin increase glucocorticoids
6. Other	decrease gastric secretions (ulcers) increase blood pressure (shock)

conducted by Day (University of Missouri) to determine if $PGF_{2\alpha}$-induced parturition for sows will reduce pig losses at birth.

The several properties of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) discussed certainly indicate potential uses by veterinarians. An outline of potential uses of $PGF_{2\alpha}$ is presented in Table 3. This list may be incomplete because new properties of the prostaglandin molecule are being continually reported. Uses in human medicine were not discussed in this paper; however, $PGF_{2\alpha}$ is beginning to be used to induce therapeutic abortions in women. This useful property of $PGF_{2\alpha}$ also can be misused, thereby forcing the FDA to strictly regulate the use of prostaglandin in animals and humans.

Presently, $PGF_{2\alpha}$, or analogs of $PGF_{2\alpha}$, are being tested in animals by clinical investigators in England and the U.S. At this time in the U.S., an INAD (Investigation of New Animal Drugs) permit must be obtained from the FDA prior to use of $PGF_{2\alpha}$.

Summary

Prostaglandin $F_{2\alpha}$ is luteolytic in cows, mares and ewes and can be used to synchronize estrus and ovulation in these species. In cattle two treatments 10 to 12 days apart synchronize ovulation such that cattle inseminated between 80 and 90 hours following $PGF_{2\alpha}$ have conception rates equal to those in control cattle inseminated at estrus. $PGF_{2\alpha}$ appears to induce luteolysis, uterine drainage and estrus in cows with postpartum pyometra.

Additional uses of $PGF_{2\alpha}$ in clinical medicine would include induced abortion, induced parturition and cases of anestrus that are caused by failure to detect estrus.

Estrus and ovulation can be synchronized in mares following $PGF_{2\alpha}$ treatment, estrus occurring three to four days and ovulation seven to eight days after $PGF_{2\alpha}$ treatment. As in cows certain other clinical cases of anestrus in mares can be successfully treated with $PGF_{2\alpha}$.

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