Update on Prostaglandin

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Introduction

Much has been said and written about prostaglandins in the past few years. Two products are now commercially available for veterinary use in mares. The efficacy of prostaglandins has been well established in cattle for estrus synchronization and now therapeutic use, especially in dairy fertility work, but as yet they are not available commercially.

Prostaglandins are unsaturated 20-carbon fatty acids whose actions on smooth muscle and blood pressure vary with their structural configuration. Prostaglandin production has been demonstrated in many tissues. They are rapidly metabolized both at the site of production and in the general circulation (Piper, et al., 1970).Prostaglandin F_2 alpha results in luteolysis, heat and ovulation when given to cattle between days 5 and 17 of the estrous cycle. Peak levels of 6 n g/ml result within ten minutes after an intramuscular injection and return to baseline levels within 90 minutes (Stellflug, Louis, Hafs and Sequin, 1975).

Kimball and Lauderdale (1975) demonstrated that the E series may be involved in stereodeogenesis via mediation of cyclic adenosine monophosphate, which seems to be the key intracellular mediator in tissue responses to hormones. Other evidence has suggested the possibility that prostaglandin functions as an intermediate in the action of luteinizing hormone (LH) (Kuehl, et al., 1970).

Several workers have shown that following intrauterine or intramuscular administration the plasma progesterone declines, plasma estradiol increases and the preovulatory LH peak occurs rather rapidly in the cow (Stellflug, et al., 1975; Louis, Hafs and Morrow, 1974).

Prostaglandin relative binding to the corpus luteum and luteolysis appear to be associated. Kimball and Lauderdale (1975) showed that, when given in low doses, prostaglandin F_2 alpha (PGF) inhibited progesterone secretion of the granulosa cells of the corpus luteum (CL). They concluded that it was not possible to be sure that PGF-induced luteolysis does not also involve some direct mechanism (e.g., reduced blood flow). Localization of the specific binding site within the CL may help resolve this question.

Therapeutic Uses of PGF

1. Synchronization of Estrus. Effective Synchronization of estrus requires the control of the life span of the corpus luteum, since the estrous cycle in the cow is controlled by progesterone secretion from the CL. This may be achieved by one of two ways: by lengthening the normal cycle with the use of exogenous progesterone or by shortening the life span of the CL with the introduction of a luteolytic agent such as PGF.

One strategy is to inject all animals initially with PGF, irrespective of the stage of cycle, and then treat all the animals again 10 to 12 days later. All animals should be within days 6 to 16 of the cycle at the time of the second injection. Cows come into estrus an average of three days later (Lauderdale, 1975; Mickelsen and DeGrofft, 1974) and ovulation occurs at about 12 hours after the end of standing heat. These cows may be inseminated at observed estrus or at 72 hours irrespective of heat signs. It appears that the single insemination works well in heifers while double insemination works best in nursing cows (Schultz, 1976). Pregnancy rates of treated animals are comparable to controls whether using PGF-Tham salt (Inskeep, 1973; Lauderdale, 1975; Oxender, 1975) or a prostaglandin analogue ICI 80,996 (Cloprostenol) (Cooper and Furr, 1975; Bailie and Dury, 1976; Hearnshaw, 1976).

In our studies, cows that were superovulated with either pregnant mare serum gonadotrophin (PMSG) or follicle-stimulating hormone (FSH) and luteolysis induced with PGF, estrus occurs earlier than those cows not previously treated with gonadotrophin. Sixty-eight and one half percent (68½%) showed estrus within two days (39 of 57). Archbald (1976) work yielded similar information. For this reason, if PGF is used to synchronize the recipient cows, treatment must begin 12 to 24 hours before the donor cow.

2. Induction of Abortion. Cattle with pathological, or normal but unwanted, pregnancy may be aborted with PGF successfully up to the fifth month of pregnancy. Doses of 45 mg or greater of PGF-Tham salt resulted in abortion of 20 of 20 cows by day 7 after injection if administered prior to day 120 of gestation. Doses as high as 150 mg were less effective when administered between days 157 and 248 of gestation (Lauderdale, 1975).

One hundred percent (100%) of the cattle (41 of 41) receiving a single treatment of 500 μg Cloprostenol aborted within the first 150 days of gestation. Nine of ten (90%) of the cows between days 150 and 200 of pregnancy aborted but required up to five treatments

(Cooper, Hammond, Barker and Jackson, 1976). We have found similar results in our studies.

Although the drug is very effective as an abortifactive agent in cattle, whether it will be used much in the feedlot for that purpose depends on whether or not the feedlot operator will get paid either by increased gains or by increased price for open heifers at the marketplace.

3. Induction of Parturition. It has been demonstrated that PGF can induce parturition, cause rapid closure of the umbilical vessels and decrease CL progesterone production (Oxender, Noden, Louis and Hafs, 1974).

Liggins, et al. (1972), proposed that, as a possible mechanism for induction of parturition, increased fetal corticoids stimulated the synthesis and release of PGF to initiate labor in ewes. Liggins (1973) also showed that PGF stimulated the release of oxytocin and potentiated the action of oxytocin on the myometrium.

Lauderdale (1975) induced parturition in 30 cows at about 267 days of gestation. Parturition occurred an average of three days after administration and all cows had retained fetal membranes for greater than two days but less than seven days.

4. Treatment of Infertility.

A. Sub-estrus. Heat periods which go undetected in postpartum dairy cows may result in failure to maintain an optimal calving interval. Heavy milking cows may show only mild symptoms of heat or may simply be missed by the farmer. This condition is referred to as sub-estrus. The cattle are usually cycling normally and may be treated with PGF following rectal diagnosis of a functional CL.

Seventy-six percent (76%) of 103 cows treated intramuscularly with 500 μg Cloprostenol showed estrus within seven days and 57% of these conceived to the first insemination (Cooper, et al., 1976).

B. Chronic Postpartum Endometritis (Pyometra). Postpartum uterine infections occasionally become chronic. When the uterus fills with pus, it is unable to initiate the normal process of luteolysis. The persistence of CL maintains the uterus under the influence of progesterone and the infection proliferates. Administration of PGF causes luteolysis which results in removal of progesterone and rapid expulsion of the uterine contents.

Cooper, et al., (1976) treated 43 cases of pyometra with Cloprostenol. Ninety-one percent (91%) responded by showing estrus within seven days. Forty-two percent (42%) of 12 cows served conceived at the first heat.

C. Mummies and Macerated Feti. Cooper, et al., (1976) used 500 μg Cloprostenol I.M. in eight cases diagnosed six months post service to six weeks beyond expected calving dates. All eight of these cases expelled the fetal remains through the cervix within five days. However, in one case, a heifer five to six months pregnant, we had a failure after two treatments.

D. Cystic Ovaries. Cystic ovarian follicles are fairly common in the cow and represent an important cause of infertility. Regression of the cystic ovarian follicles in the cow following hormonal therapy appears to involve two mechanisms. First, there is either rupture and luteinization, or luteinization without rupture. It appears the cystic follicle must first be luteinized by a luteotrophic agent before PGF will cause luteolysis. This can be accomplished with LH or PGF. Archbald (1976) showed that PGF could be luteotrophic because of its stimulating release of LH.

Cooper, et al., (1976) used Cloprostenol on 17 cows with luteal cysts. Eighty-eight percent (88%) showed heat within seven days and 47% conceived on this estrous period. We have found similar results with Cloprostenol and PGF-Tham salt.

5. Superovulation. Superovulation induced by pregnant mare sreum (PMS) for embryo transfer yields variable results. When given on day 15 or 16 of the cycle without PGF, many cows do not come into heat (Phillippo and Rowson, 1975). We found that if the donor cow does not show heat, she usually has a poor ovulation rate, thus leading to discouraging results. In cows superovulated on day 15 or 17 of the estrous cycle without PGF, 28.5% showed estrus within five days (2 of 7) and there were 32% ovulations compared to unruptured follicles (24 of 75). When PMSG was given on days 9 to 13, during the luteal phase of the cycle, and PGF given 48 hours later, 84.2% were in estrus within four days (48 of 57) and the majority on the second day. Forty-four and six tenths percent (44.6%) of these were ovulations compared to unruptured follicles (316 of 709).

Phillippo and Rowson (1975) also found the increased number of ovulations and fertile ova when superovulation was accomplished earlier in the cycle in conjunction with PGF.

6. Increased Sperm/Ejaculate. Oxender (1975) reported that bulls injected with 40 mg PGF-Tham salt one hour prior to semen collection ejaculated 20 to 40% more sperm than control bulls with sexual preparation, suggesting PGF may be potentially valuable for use in artificial insemination centers.

Conclusion

The efficacy of PGF has been established. How soon it will be available on the market for food-producing animals is not known. Since it is luteolytic in humans (Labhestwar, 1974), much work is needed in the area of dosage and clearance rates in food animals. I am sure the time is near when the veterinarian will be able to include PGF in his bovine reproductive herd health program.

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The French Ambassador

Dr. Leland Allenstein, president of the AABP (left), with Dr. E. Meissonnier, Boigneville, France. Dr. Meissonnier was the scientific organizer of the 1976 World Association for Buiatrics Congress which was held in Paris, France. He was the guest of the AABP at San Francisco.