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Clinical Applications of Prostaglandins in Dogs and Cats

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In the biological sciences today there are few substances that generate as much interest as prostaglandins. They have found widespread use in veterinary medicine, yet are only approved by the FDA for specific uses in cattle and horses. However, practical applications in the dog and cat have been reported by clinicians and have been evaluated in clinical research projects.

The purpose of this paper is, first, to provide an overview of these areas where prostaglandins may be utilized in canine and feline practice. Secondly, owing to the fact of its recent emergence on the veterinary medical scene, a brief background on prostaglandins will be included to facilitate understanding.

BACKGROUND

Prostaglandins are naturally occurring substances classified as autocooids, from the Greek *autos* ("self") and *akos* ("medicinal agent"), and referred to as parahormones, humoral mediators, or local hormones because they are not systemically circulating hormones, but act only on the local level. They are produced by most biological tissues and are detectable in most body fluids. Members of the prostaglandin family have specific reproductive functions and also participate as messenger-type agents in the function of nearly every physiologic system in the body.¹ Their actions are believed to be mediated by cyclic AMP and cyclic GMP.²

In 1936, Von Euler derived the name "prostaglandin" from the prostate gland to identify a lipid-soluble acid that he had found to be the active substance in human semen which had

previously been shown to make smooth muscle contract.^{3,4} It wasn't until 1957 that two prostaglandins (PGE₁, PGF_{1a}) were isolated in pure crystalline form and soon more prostaglandins were characterized, all of which were found to be 20-carbon unsaturated carboxylic acids with a cyclopentane ring. Thereafter, it was found that all prostaglandins are derived from linoleic and arachidonic fatty acids; arachidonate is in the phospholipids of cell membranes of all mammalian tissues.⁵

There are several main classes of prostaglandins: E, F, I, A, B, C, D, distinguished by the constituents of the cyclopentane ring. The main classes are further subdivided in accord with the number of double bonds in the side chains.³ The most biologically active compounds are PGE₂, PGF_{2a}, TXA, and PGI₂ all of which have a pair of double bonds and are, therefore, designated as the 2 series.⁵ The E and F_a Groups are the most abundant in reproductive tissues, especially PGE₂ and PGF_{2a}, with only prostaglandin F_{2a} and its analogues available commercially for veterinary use in this country. PGF_{2a} is probably the natural uterine luteolytic factor in most species.

The first product on the market was the THAM salt of PGF_{2a}, dinoprost tromethamine (Prostin F_{2alpha}^R-Upjohn Co.). It is labelled for use only in horses to control the time of estrus in cycling mares and to treat mares with prolonged diestral periods. The approved dosage is 1 mg/100 lbs. (0.022 mg/kg) administered as a single intramuscular injection. The Upjohn Co. subsequently came out with another dinoprost product (Lutalyse^R) which is identical to Prostin F_{2alpha} except it is labelled for synchronization of estrus among beef cattle and nonlac-

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tating dairy heifers, and for abortion of feedlot heifers before 100 days of gestation. The approved dosage is 25 mg as a total dose administered intramuscularly. Another commercial product is prostalene (Synchrocept^R-Diamond) which is a PGF_{2a} analogue labelled for use only in horses at a dosage of 5 ug/kg.

Besides the approved uses, PGF_{2a} is used in the bovine therapeutically for unobserved estrus, pyometra, mummified fetus, luteinized cysts, and induction of parturition.⁶ Other unapproved uses have also been recognized in the equine.^{7,8} PGF_{2a} has been used for induction of parturition in swine.⁹

Women of child-bearing age, asthmatics, and persons with bronchial and other respiratory problems should be very careful when handling this drug because prostaglandins of the F series are effective abortifacients and potent bronchoconstrictors in human beings.

Uses of prostaglandin reported in this paper are of the dinoprost tromethamine product and are in nonapproved species based solely on results of experimental use. The FDA does not sanction such uses, therefore, the veterinarian assumes full responsibility.

ABORTION

It has been established that endogenous PGF_{2a} of uterine origin in the cow is instrumental in terminating luteal function in the nonpregnant animal thus returning it to heat. PGF_{2a} release from the uterus is also important for the prepartum lysis of the corpus luteum which removes the progesterone block and for increasing the contractile strength of the uterine musculature prior to parturition.¹⁰ Consequently, exogenous PGF_{2a} has proven to be an effective abortifacient in cows. In dogs and cats it is known that prostaglandins play an important role in reproductive function but that role is not nearly as well worked out as it is in the bovine.

PGF_{2a} can be used to terminate gestation in the bitch^{11,12} and queen.¹³ One study has reported that PGF_{2a} given intramuscularly to pregnant beagle bitches from day 33 to day 53 of gestation at a dosage of either 20 ug/kg every 8 hours or 30 ug/kg every 12 hours for 72 hours (180 ug/kg total dose) will cause the fetuses to abort within 56 to 80 hours after treatment begins.¹¹ It was shown that com-

plete luteolysis was induced and abortion occurred when plasma progesterone was depressed to 0.6–1.4 ng/ml from pretreatment levels of 3–40 ng/ml.¹¹

It has been the authors' experience that the proper length of treatment (six injections, one every 12 hours) must be maintained to produce a successful abortion. In an earlier study luteolysis and abortion were not produced when a larger total dose (250 ug/kg) was given intravenously within a seven hour period.¹⁴

It also seems imperative that the treatment be delayed until the mid to late gestation period since the early corpora lutea in the bitch are more refractory to PGF_{2a}. Similarly, in cattle doses of PGF_{2a} must be given after day five of the estrous cycle in order to get luteolysis.¹⁵ An hypothesis has been proposed¹⁶ and supported¹⁷ that explains the resistance of the newly formed corpus luteum by the fact that "the preovulatory surge of LH saturates the regulatory units of the luteal cells and that it is this bound hormone which protects the young corpus luteum." Previously, corpus luteum receptors for PGF_{2a} were identified.¹⁸

It is not surprising that this regimen of exogenously administered PGF_{2a} (every 12 hours for three days) is effective in producing luteolysis in the bitch when considering the endogenous PGF_{2a} release patterns associated with luteolysis in other species. Parallels tend to appear between the natural release of PGF_{2a} and the above-mentioned regimen in dogs. In the bovine the production and release of PGF_{2a} by the uterus is known to be pulsatile and precise. During the estrous cycle PGF_{2a} is released for two to three days as rapid pulses with a duration of one to five hours prior to and during luteolysis, which is indicated by decreasing levels of plasma progesterone.¹⁹

The exact mechanism for PGF_{2a} induced luteolysis has not been worked out in any species but some theories are as follows: antagonism with LH or prolactin; promotion of fragility in lysosomes; contractile effect on the utero-ovarian vein, resulting in reduced blood flow through the ovary; decreased stores of the progesterone precursors, cholesterol esters; or decreased esterase activity.

PGF_{2a} also induces strong myometrial contractions in the bitch which plays a role in the induced abortion along with at least a decreased luteal function.

It has also been reported that a one-shot dosage of 1 mg/kg PGF_{2a} in the bitch is an effective abortifacient.¹² However, details concerning the application of this dosage are not available.

The veterinarian is often faced with the client who believes his bitch may have been bred to an undesirable male dog. The client desires that something be done to remedy the situation. If more than two or three days have elapsed since the misalliance, a mismating shot of estrogens (0.5–1 mg/lb stilbesterol or 0.5–2 mg ECP) might be ineffective or undesirable. The owner may not want the bitch spayed and would rather not put the dog through a pregnancy. In this situation a PGF_{2a} induced abortion may be indicated. First, however, the pregnancy should be confirmed by digital palpation between days 25–35 of gestation. If palpation cannot confirm the pregnancy, ultrasonography may be used as early as the 29th day or radiographs may be taken after day 42 of gestation.

If the dog is indeed pregnant and in good health, free of any respiratory problems, it can be started on a regimen of PGF_{2a} at 25–30 ug/kg every 12 hours IM or SQ for 72 hours (total of 6 treatments) starting no earlier than the 33rd day of gestation. Priming the dog with 0.1–2 mg ECP given IM about 24 hours prior to starting the PGF_{2a} treatment may increase the abortifacient effect. Although not originally described as part of the abortifacient procedure, estradiol-17B injected into ewes has elicited marked synthesis and release of endogenous PGF_{2a}.²¹ Estrogens also help prepare the uterus for contraction by increasing myometrial motility, and in some species estrogens stimulate the release of oxytocin from the posterior pituitary gland.²⁰ However, it should be stated that PGF_{2a} without estrogen priming will induce abortions.

The dog should be hospitalized and food withheld 24 hours prior to beginning the treatment regimen. In the original study¹¹ no obvious nor consistent systemic side effects were noted, but it should be expected that the dog's respiratory rate will increase, usually within five minutes after injection, and there will be vomiting and defecation. There is usually not more than one episode of emesis and defecation per injection. The panting should subside within 45 minutes. The half-life of PGF_{2a} in the body is very short being about eight minutes in the bovine.²² It has been reported

that 80% of injected PGF_{2a} is excreted in the urine within six hours in the bovine.⁴ A mild drop in body temperature (1–2°F) similar to that preceding normal parturition may be noted.¹¹ After the second or third injection the bitch may display vigorous nest building behavior. Fetal expulsions should be expected to occur approximately 56–80 hours after the first PGF_{2a} injection with the bitch showing no signs of difficulty.¹¹

Some dogs may not abort at this dosage and treatment length because of individual variability in hormonal patterns.^{11,14} This individual variability may necessitate a more flexible schedule of treatment such as a longer treatment period or higher dose. Not enough data is available to draw any statistics on the success of each possible treatment regimen.

The subcutaneous median lethal dose for PGF_{2a} in the beagle bitch has been reported to be 5.13 mg/kg.¹² At this dose the clinical signs of toxicosis include excessive salivation, vomiting, diarrhea, hyperpnea, ataxia, and pupillary dilatation and then pupillary constriction. The effects were maximal from 90–120 minutes after treatment and death occurred in a few hours (2–11). The toxicological signs resembled those of endotoxic and neurotoxic shock syndromes.¹²

Some minor side effects were noted inconsistently at dosages greater than or equal to 0.444 mg/kg given IM. These signs included: mild locomotor incoordination, rubbing the face with the forefeet, slight CNS depression, micturition and slight hyperthermia in addition to hyperpnea, vomiting, and defecation.²³ When PGF_{2a} was given IV at doses as low as 30 ug/kg emesis was caused consistently in 30 seconds and slight incoordination and illness followed.¹⁴

From the data available on side effects it is apparent that PGF_{2a} is better suited for IM or SQ injection, because it is absorbed more slowly. The most consistent side effect observed was the increase in respiratory rate which can be accounted for by the fact that PGF_{2a} is a potent bronchoconstrictor and as such should not be used in dogs with respiratory dysfunction. Vomiting also appeared often, but at the dosage of 30 ug/kg IM or SQ it does not always occur. The emesis at this dosage is not usually characterized by wrenching or illness, but occurs rapidly without much effort or discomfort on the part of the dog. The vomiting and defecation usual-

ly become less pronounced with each treatment.^{11,14} The emesis and defecation are due to the stimulatory effect of PGF_{2a} on smooth muscle.

At a dosage of 30 ug/kg there is over a 100X margin of safety (MLD = 5.13 mg/kg) which is quite acceptable. If, however, a one-injection luteolytic dosage of 1 mg/kg is used the margin of safety is only 5X, which is not acceptable. The rationale for using the larger dose is that only one injection is needed; however, it has been shown that a dosage of 30 ug/kg given every 12 hours for six treatments elicits effective luteolysis, and abortion is achieved with minimal side effects¹¹ and more closely corresponds to the body's own natural release of PGF_{2a} from the uterus prior to regression of the corpora lutea.¹⁹ Prostaglandin does not have a cumulative effect in the body because it is rapidly metabolized and excreted from the body. It is vital whenever using PGF_{2a} in the dog or cat to compute the dose accurately by weighing the patient.

In the queen it has been reported that one or two subcutaneous injections of PGF_{2a} 24 hours apart at the dosage of 0.5-1 mg/kg will induce abortion if given after the 40th day of gestation.¹³ Fetal expulsion occurred within 24 hours of the first injection or within 24 hours of the second injection, if needed. Within 15 minutes after injection cats were noted to defecate in their litter boxes. Other side effects were minimal. As in dogs, cats with compromised respiratory function should not be given PGF_{2a}.

In another study two S.Q. injections of PGF_{2a} 24 hours apart at a dosage of 0.5-1 mg/kg after the 40th day of gestation did not result in abortion, but only partial luteolysis.²⁴ Instead, after day 51 of gestation a regimen of ACTH followed by PGF_{2a} 24-96 hours later was shown to induce complete luteolysis and abortion. Using smaller doses of PGF_{2a} and spreading them out over six treatments as in the dog has not been reported in the cat.

Presently, it is not clear whether the PGF_{2a}-induced abortions in cats are due to luteolysis of the corpus luteum of pregnancy or the result of PGF_{2a}-induced myometrial contractions. Most studies have demonstrated only a partial decrease in luteal function after exogenous PGF_{2a} administration.^{24,25,26} It is likely that abortion occurred due to the "oxytocic" effect on the uterus in the presence of decreased luteal function.

A toxic dose of PGF_{2a} injected SQ has been reported in the cat at approximately 5.0 mg/kg.²⁵ Clinical signs of toxicosis noted were ataxia, respiratory distress, muscle tremors, and loose bowel movements.²⁵ The cat does not appear to be as sensitive to prostaglandins as is the dog.

INDUCTION OF PARTURITION

There have been no studies on the use of prostaglandins to induce parturition in the dog; however, since it has been shown that prostaglandins play such an important role in the normal physiology of parturition in the dog,²⁰ and since it terminates pregnancy in the mid to late phase of gestation, it seems likely PGF_{2a} alone or in combination with oxytocin, estrogen, or dexamethasone would be effective in inducing parturition. During normal parturition it has been suggested that prostaglandins may act on the pituitary gland of the dam resulting in the release of oxytocin, act on the placenta to inhibit progesterone production and release relaxin, and act on the ovary to release relaxin.²⁰

In the cat the mechanism of parturition has not been studied and hormonal interrelationships are essentially unknown, yet it is likely that the cat does not differ significantly from other species and prostaglandin alone or in combination, as in inducing abortion, may be effective in inducing parturition. In one study PGF_{2a} (0.50-1.0 mg/kg) given in two doses 24 hours apart to cats over 55 days of gestation induced parturition resulting in live kittens that were normal and healthy.¹³ The queens produced milk at parturition and suckled their young. One case report appears in the literature²⁷ where a nine-month old queen on the 70th day of gestation, with a history of a clear vaginal discharge on day 65 without obvious signs of labor, was administered two SQ injections of PGF_{2a} 24 hours apart at a dose of 0.5 mg/kg. Two hours after the second dose the first kitten was born dead and three live kittens followed within 90 minutes. The three kittens received adequate milk and were reared successfully. The queen experienced an increased respiration rate, restlessness, and incontinence during the treatment.

Prostaglandins can be used in combination with oxytocin to adequately induce labor in women.²⁸ They can also be used to effectively induce parturition in cows,²⁹ sows,⁹ does,³⁰ and ewes.³¹

PSEUDOPREGNANCY

It has been reported that 0.5 mg/kg (total dose) of PGF_{2a} given SQ to 40 clinically false pregnant bitches of various breeds and ages resulted in regression of the symptoms of false pregnancy in 37 animals.³² The symptoms included: galactorrhea, mammary enlargement, mothering behavior, nest building, and labor pains. The dogs returned to normal behavior in about seven to eight days after the treatment. The dose of PGF_{2a} had to be repeated in four cases to be effective. The side effects reported were very minimal. Presumably the effectiveness of PGF_{2a} in treating pseudopregnancy in the bitch is due to its luteolytic effect.

In the cat one study has been reported suggesting that PGF_{2a} (0.5–5.0 mg/kg SQ) given during the early luteal phase would be ineffective for the premature termination of pseudopregnancy.²⁵

SUBINVOLUTION OF THE PLACENTAL SITES

It has been reported that PGF_{2a} can be used to treat subinvolution of the placental sites in the bitch, where chronic post-partum uterine hemorrhage is a problem, by using one dose at 0.1–0.25 mg/kg or at the rate of 25 ug/kg every 12 hours until six injections have been given.⁷ The mechanism of action of PGF_{2a} in this case was not reported.

UTERINE DISEASE

Another use of PGF_{2a} in dogs is in the treatment of uterine disease. It has been reported that PGF_{2a} at 250 ug/kg SQ was used successfully in 14 of 16 cases to medically treat endometritis and pyometra.³³ Successful medical treatment resulted in remission of clinical signs within 30 days post-treatment with no surgical intervention, but supportive therapy and antibacterials were used as needed. Success was achieved in five of the six endometritis cases, in two of the three metritis cases, and in seven of the seven pyometra cases.³³ 10 out of the 16 cases needed more than one treatment, ranging from 2 to 4 treatments. The study did not report the time interval between treatments, but stated that there was "retreatment at a later date." All but one of the pyometra cases appeared to be open pyometras. In a follow-up of nine intact bitches to assess post-

PGF_{2a} fertility all nine had a subsequent estrus period. Five of nine bred at an estrus after treatment were subsequently pregnant. Two of the five whelped normal litters. It did not state the outcome of the other three pregnant bitches. The study suggests that PGF_{2a} therapy may offer an alternative to surgery in breeding bitches, in cases where surgery may not be desired by the pet owner, and in animals that might otherwise be questionable surgical risks.³³

Two case reports on the use of PGF_{2a} to treat pyometra in the bitch appear in the literature. In one case an open pyometra in a two year old basset hound was treated with one IM injection of PGF_{2a} at a dose of 0.2 mg/kg after an unsuccessful therapeutic course of antibiotics.³⁴ The dog subsequently exhibited the typical prostaglandin side effects of restlessness, panting, nest building, and it vomited once. Within 60 minutes a purulent discharge appeared from the vulva that became progressively more mucous in nature over a period of nine hours. In the subsequent estrus period the dog was mated and produced nine healthy puppies.

The other case was described as a typical closed pyometra and was treated with one SQ injection of PGF_{2a} at a dose of 0.25 mg/kg. Within 17 hours approximately one gallon of purulent mucous discharge had been evacuated.²⁷ Oxytocin was thereafter administered which was followed by an increase in discharge for a few hours. The vaginal discharge reoccurred 13 days later and was treated with two doses of PGF_{2a} (0.25 mg/kg SQ) given 24 hours apart, followed by antibiotics. The discharge did not reoccur.

One report appears in the literature on the ineffectiveness of prostaglandins for treatment of uterine disease.³⁵

EMESIS AND DEFECATION

One possible nonreproductive use of PGF_{2a} has been reported.²³ It was suggested that PGF_{2a} could be used for the clinical induction of vomiting and large intestine evacuation in the dog. Defecation (83.3% of dogs) without vomiting occurred in dogs given a dosage of 0.111 mg/kg. Emesis (87.5% of dogs) and defecation (75% of dogs) were observed in dogs given a dosage of greater than or equal to 0.444 mg/kg with emesis occurring 1.6 to 2.6 minutes after defecation.

In effect, this use of PGF_{2a} is taking advantage of the side effects of prostaglandin reported in reproductive applications. However, the one major side effect that always appears even before vomiting and defecation is the increased respiratory rate, so respiratory function would have to be carefully ascertained before PGF_{2a} use. The dosage would also have to be accurately calculated to avoid other undesirable effects. Possible advantages to the use of PGF_{2a} to induce vomiting and defecation are its rapid action, injectability, and availability for the mixed practitioner when an emergency emetic is needed in the field.

Many potential nonreproductive veterinary clinical applications of prostaglandins have been suggested and initially investigated.⁵ The prostaglandins involved include PGF_{2a}, PGE₁, PGE₂, PGI₂, and many varied prostaglandin-active agents such as aspirin, phenylbutazone, flunixin meglumine, theophylline, vitamin E, selenium, and isoproterenol. The scope of these potential uses is broad and encompasses the treatment of the following: disseminated intravascular coagulation; endotoxemia; chronic vascular disease, such as cardiomyopathies; ischemia and sequelae, such as shock, and laminitis; excessive bleeding; bronchial asthma; toxic hepatitis; and neoplastic metastasis.

The veterinary clinician should be aware of the uses of prostaglandins that are currently applicable as they may offer a source of viable therapy or alternative treatment in small animal medicine. In order to use prostaglandins properly, with minimal deleterious untoward effects and successful administration, a basic understanding of their mechanism of action, physiological effects, and metabolism is absolutely necessary. Recent advances in prostaglandin research have made nonreproductive veterinary uses potentially available and the future portends further medical advances based on prostaglandin physiology.

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