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Practical use of hormones in small animal reproduction

Uso clínico de hormônios na repodução de pequenos animais

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Abstract

The abortifacient efficacy of prostaglandin F2alpha products (PGF) involves induction of luteolysis, stimulation of uterine contraction and cervical dilation. PGF will induce luteolysis and depress progesterone (P4) concentrations to nearly non-detectable levels very easily after day 25 or 30 following just a 4-5 day course of treatment. PGF can be used also earlier in pregnancy provided that the onset of cytological diestrus is timed precisely and treatment course is longer than 5 days. With late abortion, the treatment must be continued until verification of efficacy by ultrasound as partial abortion of litters can occur. Other uses of PGF include shortening of diestrus in bitches, emptying the uterine content and improving semen quality in dogs. Anti-prolactin agents include dopamine agonists (bromocriptine or cabergoline), and serotonin antagonists (metergoline). Anti-prolactin drugs can be used to control pseudopregnancy, induce abortion and the resumption of estrus. Antiemetic (metoclopramide and domperidone) and antipsychotic drugs (chlorpromazine and sulpiride) have prolactin release properties which are widely documented in human medicine; their clinical efficacy in the treatment of agalactia or hypogalactia is anecdotally reported also in bitches and queens. Aglepristone saturates P4 receptors causing abortion when administered at the dose of 10 mg/kg twice 24 hours apart. The early administration of aglepristone at 0 to 25 days after mating is approximately 99% effective in prevention of pregnancy; however, care should be taken when using it without having assayed serum P4 or after day 35 of pregnancy. Aglepristone can be used for several other purposes among which induction of parturition and treatment of feline mammary hypertrophy. The clinical use of other hormonal drugs such as estrogens and sympatho-mimetics for conditions such as urinary incontinence and retrograde ejaculation is briefly discussed.

Keywords: Homonal theraphy, dogs, cats.

Prostaglandins

Several Prostaglandin F2alpha (PGF) compounds have been available for half a century as veterinary compounds for use in food animals and horses. Their luteolytic and uterotonic actions make them unique, and very useful also in small animals, although no pharmaceutical company has yet even taken into consideration marketing a prostaglandin product for use in dogs and cats. Recently, the use of human prostaglandin E (PGE) products has started to diffuse among small animal practitioners. PGF compounds can be used in small animals with the following indications:

Early pregnancy termination in bitches

The abortifacient efficacy of prostaglandin F2alpha products (PGF) involves induction of luteolysis, stimulation of uterine contraction and cervical dilation. In dogs, the P4 supporting pregnancy is entirely from the corpora lutea throughout gestation. PGF will induce luteolysis and depress P4 concentrations to nearly non-detectable levels very easily after day 25 or 30 following just a 4-5 day course of treatment. PGF can be used also earlier in pregnancy provided that the onset of cytological diestrus is timed precisely and treatment course is longer than 5 days (see Table n° 1). The later in the cycle PGF is administered, the easier and more rapidly the induction of luteolysis. Use of natural PGF compounds requires subcutaneous administration 2 or 3 times a day, for 6 days or longer while most synthetic analogues may be given once daily (Tables 1 and 2). The dosage varies depending on the type of PGF: natural PGF should be given a maximum dosage of 80 mcg/kg at least twice (but can be given 3 times) daily, starting gradually with 1/3 to ½ the dose for the first day (or the first 2 administrations); cloprostenol is currently being used at a dose of 1 mcg/kg (once every 24-48 hour intervals) while alphaprostol may be used at the dose of 20 mcg/kg twice daily like natural PGF. Side effects (which include emesis, salivation, defecation, urination and slight tachipnea) are dose dependent (displayed in 75% of bitches using doses of 250 mcg/kg natural PGF and only in 25% of bitches using doses of 50 mcg/kg natural PGF) and self-limiting, decreasing in intensity with repeated dosing.

Regardless of the drug used, each bitch should be given a thorough physical exam to make sure her cardiopulmonary system is in good conditions. Because of their low therapeutic ratio, PGF products should be administered in the clinic and not prescribed for home use by the owner. Also, as efficacy of each early abortive product is at best 80-90%, it is very important to perform a uterine ultrasound at the end of treatment: if a

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pregnancy is diagnosed at this time, another treatment cycle (with PGF) can be instituted. Whenever an early pregnancy termination is performed, anestrus may be shortened and therefore return to oestrus may be anticipated. The simple scheme on Table 1 summarizes 3 fundamental steps for performing an early abortion in the bitch.

Table 1. Treatment protocol using a natural PGF compound to induce early pregnancy termination in the bitch following an unwanted mating. Abortifacient treatments do not need to be started exactly on day 8 but can be started as late as day 9 or 10. This allows for some flexibility as a therapy can be initiated on a Monday instead of during the weekend.

Identify D1 through sequential vaginal smears every 2-3 days
• Wait 8-10 days (therefore until 14-16 days post-ovulation) • Administer natural PGF2, 80 mcg/kg BID SC for at least 6 days as follows: 50 mcg/kg on day 1, am and pm 65 mcg/kg on day 2, am and pm 80 mcg/kg on day 3 and followings, am and pm • Perform uterine ultrasound on the last day of treatment

Late pregnancy termination in bitches and queens

Canine late pregnancy termination is generally adopted as a treatment when either a mismating was not observed, the female was not in the ovulatory phase or fertility of the male is unknown. In cats, the result of a serum progesterone assay done on a blood sample collected within 3-7 days following mismating can be used as an indirect indication of pregnancy, as ovulation is induced in this species. Dosage of PGF compounds is the same as for early abortion, the only difference being that treatment must be continued until verification of efficacy by ultrasound as partial abortion of litters can occur if treatment is discontinued prematurely. With most dosages, 9 or more days may be required to terminate some pregnancies, although 5 to 7 days is usually sufficient. A study of 67 pregnant bitches demonstrated a 100% efficacy in termination of pregnancy using cloprostenol at the dose of 2.5 mcg/kg subcutaneously, administered three times, at 48 h intervals, starting at day 30 of pregnancy. Cloprostenol at even lower doses has been used in combination with dopamine agonist treatment to terminate pregnancy in dogs shortly after implantation (which in bitches and queens occurs around 15-18 days after ovulation) starting around day 23 from ovulation. Although the use of premedication with atropine sulphate or prifinium bromide is reported prior to administration of natural PGF compounds, we have never used it and feel that its use is almost always unnecessary. Mismated queens can be treated with natural PGF at a dose of 2 mg/cat IM once a day, beginning at day 33 of pregnancy, as this will induce luteolysis and terminate pregnancy by expulsion of fetuses in pregnant cats. Side effects included prostration, vomiting and diarrhea. The PGF analogue cloprostenol has been successful for mid-pregnancy termination in combination with cabergoline also in cats.

Shortening of diestrus in bitches

The use of a 6-10 day course of PGF starting after day 10 of cytological diestrus will effect luteolysis. The consequent reduction of the length of the luteal phase wil cause a shortening of anestrus. We have observed bitches treated with PGF early in their luteal phase coming back in heat after 70-90 days following the onset of proestrus. If a PGF treatment (shortening the duration of diestrus) is then followed by a cabergoline treatment (shortening the duration of anestrus), the interestrous interval can be substantially shortened. We have succeded in significantly shortening the duration of interestrous interval in a kennel of Rough Collies using this technique thus increasing the number of litter/year.

Emptying of uterine content in bitches and queens

The mioconctracting action of PGF compounds is well known, and can become useful when dealing with open-cervix pyometra or late abortion with incomplete fetal expulsion. Dosage are the same as listed above. We frequently use PGF compounds combined with aglepristone when late pregnant bitches are presented for induction of abortion, as such combined treatments are shorter and more efficacious. Care should be taken to make sure that the cervix is open, as causing uterine contractions on a closed cervix may cause uterine rupture or force uterine content up into the oviducts. With closed cervix pyometra aglepristone is the only alternative to surgery. administered first (see over) and then PGF are used once uterine evacuation has started.

Improving semen quality in the dog

The use of PGF at the dose of 100 mcg/kg 15 minutes prior to semen collection results in an increase of 270% of total sperm numbers when compared to saline treated controls, with no deleterious effect on refrigeration and freezing. PGF can also be used to obtain an ejaculate from a reluctant or inexperienced dog.

PGE

Misoprostol is a type E prostaglandin (PGE) marketed as a human compound to protect the gastric mucosa when using a chronic treatment with a non-steroidal anti-inflammatory drug. It is marketed under different trade names in different European countries (i.e. Cytotec™ (France/Italy/Spain), Misodex 200™ (Italy), or Menpros™ (Spain), and is available in 200 mcg tablets. In the bitch it is administered at 10 mcg/kg BID orally (1/2 tablets/10 kg) (Tab. 2). Misoprostol is characterized by a strong uterine contracting action which has been tested in dogs and cats with pyometra and for which it appears to be effective in causing evacuation of uterine content, although it does not have any luteolytic properties. Misoprostol is gradually replacing PGF2a compounds in dogs and cats with pyometra because it is marketed in pills and therefore can be prescribed and administered at home by the owner, and also it has no side effect both in species.

Table. Dosages of the most commonly used prostaglandin compounds in bitches and queens to induce luteolysis and cause uterine contractility. Prostaglandins should never be used to treat a closed-cervix pyometra because of the risk of uterine rupture or pushing uterine pus retrogradely into the uterine tubes and through these into the abdominal cavity. When treating a female with any prostaglandin, start with half the normal dosage and gradually achieve the full dose within the first 2-3 days of therapy.

Prostaglandin	Dose Bitch	Dose Queen	Route and timing of administrations
PGF2α (Natural PGF2α - Dinoprost)	50-80 mcg/kg	80-100 mcg/kg	2, SC 2, SC
PGF2α (Cloprostenol)	1 mcg/kg	1 mcg/kg	1, SC
PGF2α (Alphaprostol)	20 mcg/kg	20 mcg/kg	2, SC
PGE (Misoprostol)	10 mcg/kg	50-100 mcg/cat	2, per os

Antiprolactinics

Prolactin secretion by the lactotroph cells of the anterior pituitary gland is regulated by multiple neuro-transmitters and hormones, with the major control mechanism being the activation of prolactin-inhibiting dopaminergic neurons in the hypothalamus. Prolactin is a major luteotrophic hormone and appears to be an absolute requirement for canine and feline progesterone secretion by day 30 after ovulation. Dopamine agonists like bromocriptine or cabergoline are ergot alkaloids, with strong dopamine D2-receptor agonist activity, and thus can reduce prolactin secretion thereby suppressing progesterone levels. The seretonin antagonist metergoline stimulates endogenous dopamine secretion and thus can inhibit prolactin secretion as well.

Cabergoline has a slow clearance, which allows for a single oral daily administration. Furthermore, its action is longer than 48 hours due to its particularly long (minimum 48 hours) half-life at the hypophyseal level. Because of its more specific D2-type action, cabergoline presents only few side effects when used at clinical dosages. Bromocryptine mesylate inhibits PRL secretion during relatively short periods of time (half-life: ± 4-6 hours) and in a dose-dependent mode. In order to effectively inhibit PRL tone in a continuous fashion for therapeutic purposes, bromocryptine should be administered at least twice a day, administered orally at doses 10-50 µg/kg. Its lack of specificity leads to side effects on the cardiorespiratory system, causing hypotension due to vasodilatation (adrenergic type effect), or emesis due to stimulation of the Chemioreceptive Trigger Zone (CTZ).

Metergoline is essentially a serotoninergic antagonist with dopaminergic agonist properties when used orally at doses of 0.1 mg/kg BID. Its shorter half-life requires at least twice daily administrations. Its antiserotoninergic properties can induce marked central effects such as depression, nervousness, increased excitability, changes in appetite (anorexia or bulimia), psychotic effects (escaping from home, aggressiveness). Gastrointestinal side effects due to stimulation of the CTZ are characterized by vomiting in 50% of the bitches. Emetic side effects of cabergoline and bromocryptine are identical. However, when considering dosages commonly used in a clinical setting, the emetic effect of bromocryptine is almost always present while it is negligeable with cabergoline. Therefore, emetic effects are sometimes observed when using metergoline, especially when overdosing it. Antiprolactinic drugs can be used in the bitch and the queen with three indications: pseudopregnancy, induction of abortion and induction of estrus.

Pseudopregnancy

The anti-lactogenic action of both metergoline and cabergoline is well kinown. Their administration for 4-5 days at pharmacological doses is effective in treating pseudopregnancy signs and reducing milk production. Occasional failures can be dealt with by repeating the treatment protocol and extending it to 8 to 10 days, and also by administering at the same time metergoline (at the usual antigalactogenic dosage of 200 mcg/kg BID) or bromocriptine (10-30 mcg/kg BID). Antiprolactinics are currently considered the treatment of choice for pseudopregnancy. Until the last part of last century, when antiprolactinics became commercially available, progestogens were thought to be an appropriate treatment for false pregnancy due to their lowering action on PRL concentrations at the end of the luteal phase; infact, progestogen administration is clinically demonstrated to be effective in preventing the occurrence of lactation and of pseudopregnancy as well as in eliminating related clinical signs. However, a rebound effect is frequently observed following treatment withdrawal, similarly to what occurs at the end of a normal luteal phase, when the progesterone decline triggers a PRL peak. Therefore, progestins should not be used as a treatment for false pregnancy.

Induction of abortion

The abortion induction properties of antiprolactinic drugs have been well studied for cabergoline, while not as much is known for metergoline. Cabergoline is effective in terminating pregnancy in dogs when administered at mid-gestation (as prolactin secretion starts around day 25) or later. When administered after day 40 at doses of 5 mcg/kg, PO, for 5 days cabergoline is effective in causing abortion in all bitches treated. If cabergoline administration is started earlier in pregnancy, at day 25, treatments that are effective later in pregnancy fail in most bitches and pregnancy may continue unless terminated by retreatment. Cabergoline produces little if any side affects at pharmacological doses. Combination treatment of cabergoline and prostaglandins have been used for induction of late abortion both in bitches and queen. Treatments include alternating drugs on consecutive days, and are knon to be quite effective especially since the dosage of PGF can be reduced.

Estrus induction

The estrus inducing action of antiprolactinic drugs was initially thought to be due to the lowering of prolactin concentrations, but studies done at Utrecht have demonstrated that shortening of anestrus occurs irrespective of prolactin concentrations. All the 3 antiprolactinic products (cabergoline bromocriptine and metergoline) have been used for oestrus induction in the bitch. Cabergoline and bromocriptine have consistently given positive results, while metergoline's results have been more variable depending on dosage. Using low dose (0.1 mg/kg BID) of the commercial oral preparation of metergoline administered from 100 days after ovulation until the following proestrus, the interoestrous interval can be significantly shortened. The administration of bromocriptine in anoestrus will induce oestrus within 28-50 days. We have used bromocriptine at the dose of 10-25 mcg/kg in 5 bitches with prolonged anoestrus: 4/5 came in oestrus within 13-28 days, and all 4 conceived and whelped. Using cabergoline (5 mcg/kg, once daily for up to 28 days) or natural PGF (80 mcg/kg SC, BID for 5 days starting on cytological dioestrus day 10) we achieved an interoestrous interval of 6 months in 6 treated bitches as opposed to an interval of 9 months in 9 control bitches. We have also used cabergoline (5 mcg/kg, once daily for up to 28 days) in 9 bitches (7 Rough Collies, 1 Shetland sheepdog and 1 English Setter) for a total of 11 cycles: fertile oestrus was induced in 10/11 cycles in 24 $\pm$ 11 days with a reduction of the interoestrous interval of 1.8+0.2 months. In our experience, the clinical use of antiprolactinics to induce oestrus has proven to be safe and highly effective. Side effects are minimal (particularly with cabergoline), being mostly related to the gastrointestinal tract (nausea, rare vomiting) with no other reproductive effect.

Lactogenetic drugs

Antiemetic and antipsychotic drugs have prolactin release properties, which are widely documented in human medicine, and for which are employed in the treatment of agalactia or hypogalactia. The same effects are anecdotally reported in bitches and queens.

Antiemetics

Metoclopramide is a central nervous system (CNS) dopamine D2 receptor antagonist used as a human antiemetic drug. Recommended dosages for galactogenic effect in women are 10-15 mg/day 3 times daily (TID), per os for 3-4 weeks. Its antagonizing action on the main PRL inhibitor dopamine causes a powerful, albeit indirect stimulus to PRL release with reported high efficacy rates especially when metoclopramide is associated with oxytocin nasal spray. In lactating women, metoclopramide is transferred to breast milk where it quickly

becomes more concentrated than in plasma (milk-to-plasma ratio of 1.8:1), although this is not regarded as critical for babies since the milk level is below pharmacological doses. Metoclopramide acts also as an antagonist of serotoninergic receptors (although this does not prevent PRL-releasing action), and has some cholinergic effects on smooth muscle. Maternal side effects include tiredness, headache, anxiety, nervousness and intestinal disorders. At higher doses (2-5 mg/kg) the drug may penetrate the blood-brain barrier and extrapyramidal signs (anxiety, agitation, movement disorders, dystonic reactions, ataxia) are reported.

Metoclopramide is also normally used in dogs as an antiemetic drug at oral dosages between 0.2-0.4 and 1-2 mg/kg divided in 2-3 administrations. It has been used also to stimulate canine PRL secretion, although scientific data with pre- and post-treatment PRL concentrations are available only for male dogs, in which a significant increase in serum PRL concentration is reported following treatment with 0.2 mg/kg 3 times daily. Use of metoclopramide in bitches with agalactia is anecdotal, with protocols varying from low (0.2-0.5 mg/kg SC or PO, BID or TID) to high dose regimens (1-5 mg/kg beginning PO or SC, every 6-8 hrs). Efficacy seems to be adequate with (subjective) improvement of milk production in ≥50% of cases, although no data on PRL concentrations pre- and post- treatment is available. Extrapyramidal signs may occur in canines, and are a concern in nursing bitches, therefore higher dosages should best be avoided. Improvement in milk production is generally noticeable within 24 – 48 hours. To minimize side effects, it is advisable to start at a lower dose (0.5 – 2 mg/kg/day divided TID) for the first 24-48 hours and then if there is no improvement gradually increase the dose every other day until an effect or abnormal clinical signs are noted, at which point the dose is dropped to the prior days dose or discontinued. Extrapyramidal signs are much more common at doses above 2 mg/kg/day. Bitches should be monitored carefully when being treated with metoclopramide to ensure injury to the pups does not occur. Treatment should be continued for at least 2-3 days beyond when milk production appears to be resulting in adequate daily weight gain for the pups without supplementation.

Domperidone is a peripheral dopamine receptor antagonist developed as an antiemetic agent and used for the treatment of nausea and vomiting. In women, domperidone significantly increases PRL secretion thereby enhancing breast milk production, and is therefore used (off-label) as a galactogogue in most Western countries. The maximum approved treatment protocol of domperidone in lactating women is 20 mg given 4 times daily, although most authors advice using doses of 10 mg orally TID for 1-2 weeks. However, the minimum effective dose and the minimum duration of therapy have not been identified yet. Domperidone causes a significant (75%) increase in serum PRL concentrations and milk production in treated vs control mothers. Unlike metoclopramide, domperidone is less permeable to the blood-brain barrier and is transferred in moderate quantities to maternal milk (milk-to-plasma ratio of 0.2-1.1), due to its high molecular weight and its 90% binding to plasma proteins. No side effects are reported in infants of mothers taking domperidone, while side effects in mothers include oral mucosal dryness, skin eruption, itching, headache and gastrointestinal disorders; extrapyramidal effects have been observed (dystonia) but are rare. No difference in milk quality of mothers treated with domperidone is reported, except for significant increases in carbohydrate and calcium.

Early experimental use of domperidone has been reported in the dog, with data on pharmacokinetics and excretion and metabolism in Beagle dogs. However, there is a lack of scientific as well as anecdotal information on clinical use of domperidone in small animals with low milk production. This is surprising given the positive results and the lack of side effects of this drug making it probably the best treatment for increasing milk production in lactating mothers. Domperidone is known among small animal clinicians by “word of mouth” to be effective in improving milk yield at doses of 1.5-2.0 mg/kg in queens, and 2.2 mg/kg in bitches, per os for 1-3 weeks. Treatment should be continued for at least 2-3 days beyond when milk production appears to be resulting in adequate daily weight gain for the pups without supplementation. In our experience, results of domperidone in increasing milk production in agalactic bitches and queens appear to be positive, better than those obtained with metoclopramide and devoid of extrapyramidal effects. Diarrhea is the most common side effect in the bitch, although there are anectodal reports of behavior changes in some bitches being medicated.

Antipsychotics

Chlorpromazine is an antagonist of D2 dopaminergic hypothalamic receptors, commonly used for the treatment of human psychosis including schizophrenia and depression. It is considered the prototype of the phenothiazine class of drugs. Its action on dopaminergic receptors causes PRL release, which is the reason for its off-label use in breastfeeding mothers. It is transferred to milk in low quantities (milk:plasma ratio of 0.5), and its recommended dosage for galactogogic effect is 25 mg orally TID for one week. Chlorpromazine has a wide action on different CNS receptors producing also anticholinergic, antihistaminic, as well as weak antiadrenergic effects. The main side effects of chlorpromazine in psychotic patients (who are treated with higher doses than lactating mothers) are mostly due to its anticholinergic properties and include sedation, slurred speech, dry mouth, constipation, urinary retention, possible lowering of the seizure threshold, increased appetite and impaired glucose tolerance leading to increase in weight. Not much is known about side effects of chlorpromazine in breastfeeding mothers and their infants, although lethargy, sleepiness and reduced activity have been reported in a few babies.

In small animals, chlorpromazine is used as a second choice antiemetic drug when metoclopramide does not work and blood pressure is normal. Suggested antiemetic dosage is 0.2-0.5 mg/kg every 6-8 hrs. Only anecdotal information on the use of chlorpromazine in cases of agalactia is available for small animals. Some authors advice the use of acepromazine at 0.125-0.5 or 0.5-2.0 mg/kg, SC 2-3 times/daily. No data on clinical efficacy in bitches or queens as well as milk:plasma ratio of transfer are available for this drug.

Sulpiride is a substituted benzamide used as an antipsychotic drug for the treatment of human psychosis including schizophrenia and depression. It is a strong antagonist of serotoninergic receptors as well as of muscarinic, alpha-adrenergic and histaminic receptors. Its administration (off-label) to breast-feeding women in galactogenic doses of 50 mg orally 2-3 times/day for 1-4 weeks produces a strong PRL-releasing effect with PRL reaching serum concentrations which may be up 90% higher than in the control group and infants of treated mothers gaining significantly more weight than control ones. Significant increases in milk production are reported only for primiparous mothers, not multiparous. Milk of treated mothers shows presence of the drug, although the milk:plasma ratio of transfer is lower than with metoclopramide or chlorpromazine. Although side effects are extremely rare in mothers and have never been reported in infants of treated mothers, the AAP advises against use of sulpiride in breastfeeding women as it does with all neurotropic drugs.

Progesterone antagonists

Aglepristone can be used for:

Early and late pregnancy termination in bitches and queens (this is the only official indication)

The early administration of aglepristone at the dose of 10 mg/kg twice 24 hours apart 0 to 25 days after mating is approximately 99% effective in prevention of pregnancy. However, early pregnancy termination with progesterone receptor blockers should be done cautiously as in order to be effective aglepristone requires a serum progesterone concentration to be present. Although the leaflet states that it can used between day 0 and 45 it is probably best to *make sure that in early pregnancy corpora lutea are present* by assaying serum P4 (if the bitch has not ovulated yet the drug may start decreasing its concentration in the general circulation when P4 starts being secreted). The later administration of aglepristone, at Day 26 to 45 after mating induces resorption or abortion within seven days in approximately 95% of cases studied. However, it is best to *avoid treating with aglepristone alone bitches who are pregnant beyond day 35*, as foetus/es after 45 days may occasionally survive treatment and either be born/expelled live around day 53-55 or die and not be expelled from the uterus. Treatments with aglepristone can be started after day 35 provided that the issue is thoroughly discussed with the owner, including the possibility that a PGF treatment is associated to help evacuating the uterus.

Antiprogestins in cats: Aglepristone can induce abortion in cats. The suggested dosage is higher than in the dog, being 15 mg/kg twice 24 hrs apart.

Open and closed-cervix pyometra in bitches and queens

Conservative medical treatment of bitches with pyometra can be achieved with the administration of 10 mg/kg of aglepristone on days 1, 2, 8 and then also 15 and 28 depending on the clinical situation in bitches with both open cervix and closed-cervix pyometra. The use of aglepristone should be associated with specific antibiotics if necessary, and can also be associated with PGF provided that cervical opening has occurred. In bitches with closed cervix pyometra, administration of aglepristone is often followed by cervical opening within 24-48 hrs. There is no information on the effect of aglepristone on pyometra in the queen, but efficacy for this indication is thought to be the same as in dogs.

Induction of parturition

Parturition has been successfully induced in the bitch on day 58 day of gestation using Aglepristone alone at the dose of 15 mg/kg. Gestation length was shorter in treated vs control bitches (59 vs 62 days). Fontbonne and coworkers used a combined AGL+Oxytocin treatment: one injection of aglepristone at the dose of 15 mg/kg was administered on day 59-61, and then starting 24 hrs later oxytocin was administered at the dose of 0.15 IU/kg every 2 hr. Parturition began approximately 30 hours after the Aglepristone injection (from 9:00 to 12:00-18:00 of the following day) and resulted in the birth of puppies which were alive and viable at 1 month. Length of parturition, expulsion time and incidence of neonatal mortality is normal. However, 2 small size treated bitches delivered some of their pups before the first administration of oxytocin; furthermore, 4 Yorkshire terrier pups (treated group) were born premature and died at 19-29 hr after birth. This can be an interesting protocol for induction of parturition in bitches if these results are confirmed, but more studies are necessary to highlight potential risks for the dam and neonates.

Aglepristone can also be used in the planning of an elective caesarean section, particularly if surgery needs to be done prior to physiological termination of pregnancy because of fetal death, or in case of prolonged singleton pregnancy. Levy et (2009) administered one injection of 15 mg/kg AGL 59-60 days post-ovulation. C-section was performed 20-24 hours after treatment. There were no post-operative complications and no signs of prematurity in all pups. 5/188 pups died during the first 2 weeks of life (2.6%). Serum P4 remained > 2.0 ng/ml at time of surgery, which would justify the use of AGL as a high serum P4 concentration following a C-section would delay uterine involution.

Treatment of feline mammary hypertrophy

Benign mammary hypertrophy is a benign fibroglandular proliferation of one or more mammary glands which typically occurs in young queens at their first luteal phase. The proliferation of the mammary gland is due to an excessive response to the action of P4 which is present in presumably normal concentrations in affected animals. Mammary glands will start swelling rapidly and within 2-3 days all glands become very swollen, firm and nodular. If left untreated, the problem may disappear on its own without any complication in most cases. Treatment with prostaglandins or antiprolactinic is not effective, while removal of ovaries or administration of aglepristone can be curative. When mammary hypertrophy occurs following progestogen administration, signs typically do not subside immediately following neutering or withdrawal of progestin therapy. In such cases, surgical removal of persisting nodules should be considered in order to perform histology and rule out presence of neoplasia. Dosages for mammary hypertrophy may need to be higher (i.e. 15 mg/kg) or prolonged in time depending on whether it is a spontaneous disease or if it is due to progestogen administration. Recently, Muphung et al (2009) studied the effect of aglepristone in a group of queens treated with a high dose of medroxyprogesterone acetate (MPA - 50 mg) followed by 2 injections of 10 mg/kg aglepristone 3 weeks later. Based on histology and immunohistochemistry, no evidence of an effect of aglepristone on the mammary gland of treated queens was present. Lack of effect might be due to the very high dose of MPA used, to the rather low dose of aglepristone (10 mg/kg instead of 15 mg/kg), to the short treatment with aglepristone (only 2 injections) or to the long interval between MPA and aglepristone treatments.

Sympathomimetic drugs

The clinical effect of drugs in this category is enhancement of urethral closure through the release of endogenous norepinephrine and direct stimulation of alpha-adrenergic receptors in the bladder neck and urethra. Thanks to such action, alpha-agonists can be used for the treatment of urinary incontinence and retrograde ejaculation.

Urinary Incontinence

Sympathomimetic drugs

These drugs typically have a rapid onset (within a few days) and high degree (75-90%) of efficacy in causing urethral closure through the release of endogenous norepinephrine and direct stimulation of alpha-adrenergic receptors in the bladder neck and urethra. The following is a list of alpha-adrenergic drugs and related dosages which have been used to treat canine urinary incontinence.

- Phenylpropanolamine 0.5-4.0 mg/kg TID
- Ephedrine 1.0-4.0 mg/kg BID
- Pseudoephedrine 15 (<25 kg bw)-30 mg (>25 kg) TID
- Phenylephrine 0.1-0.3 mg/kg IV
- Imipramin 5-15 mg/dog per os BID (1 mg/kg TID *)

In some European countries phenylpropanolamine is marketed as a veterinary product, while in most other countries human preparations can be used to treat this problem in dogs and cats. The dose range for most alpha-agonist drugs varies between 1.0 and 3.0 mg/kg, orally, 1-3 times daily. Phenylpropanolamine and ephedrine are currently regarded the most effective among the alpha-agonist drugs. Treatment success in a recent blinded, placebo-controlled trial in which phenylpropanolamine was administered at the dose of 1.0 mg/kg was 85% (full success) plus a 15% of significant improvement, while it was 33% and 14% in placebo treated bitches, respectively. The right dosage should be established for each individual case: start with a low dose and titrate up until a good efficacy is reached. Side effects are rare and include anorexia, weight loss, hyperexcitability, restlessness, tachicardia, skin eruption

Retrograde ejaculation

The canine bladder neck has a rich cholinergic and adrenergic innervation. Cholinergic stimulation produces gradual contraction of the neck as well as of the whole bladder (occurring during micturition), while adrenergic stimulation occurring at ejaculation causes contraction of the neck and relaxation of the body of the bladder. Improper functioning of the bladder neck at ejaculation may cause the sperm rich fraction to flow retrogradely into the bladder following the path of least resistance. Retrograde ejaculation has been reported in the dog. Sympathomimetic agents such as ephedrine, pseudoephedrine hydrochloride, phenylpropanolamine and imipramine are generally used (alone or in combination) to treat human retrograde ejaculation. Treatment protocols employing sympathomimetic drugs reported in the dog include phenylpropanolamine (3 mg/kg per os) and pseudoephedrine hydrochloride (3-5 mg/kg per os) to be administered 3, 1 and 0.5 hours prior to breeding/semen collection).

Side effects of alpha-agonists are rare in the average dog, and include anorexia, weight loss, hyperxcitability, restlessness, tachicardia, skin eruption. Some human preparations of alpha-agonists are combined with antihistaminic drugs (chlorphenamine, pheniramine, mepiramine, dyphenylpyraline etc.) which may cause dryness of the oral mucosa as well as drowsiness, and some others include also caffeine. Although the clinical effects of these combinations in small animals is unknown, side effects of antihistaminic drugs and of caffeine should not be a cause of concern except in dogs with cardiac problems. Phenylpropanolamine is available in several European countries as a veterinary product, as an oral preparation for incontinent bitches (Propalin, Vetoquinol).

Estrogens

Estrogens have always been considered as potentially dangerous drugs because of their role in inducing mammary neoplasia and bone marrow aplasia in women as well as in bitches. However, only long-acting synthetic compounds such as diethylstilbestrol, estradiol, estrone and other esther compounds are characterized by such dangerous action because of their prolonged nuclear occupance time in estrogen receptors of target tissues. Short-acting estrogenic compounds such as estriol are not characterized by the development of full estrogenic side effects.

Urinary incontinence

Steroids

The following is a list of estrogens and related dosages which have been used to treat canine urinary incontinence.

- 17-beta estradiol 0.01 mg/kg MID sc/im for 3 days
- Estradiol benzoate 0.01-1.0 mg MID per os
- Estradiol valerate 1.0 mg/10 kg bw
- Diethylstilbestrol 0.06 mg MID, tapering out to 0.01 mg
- Estriol 0.5-2.0 mg
- Conjugated estrogens 0.02 mg/kg

Estriol is considered a safe drug due to its short-action which is characterized by short nuclear occupance time and minimal metabolism following absorption. Estriol does not bind to sex-hormone binding globulin, which helps in preventing development of full (late) estrogenic effects such as endometrial hyperplasia, pyometra and bone marrow suppression. Estriol has been used for decades in women in hormone replacement therapy, and is marketed as a veterinary preparation to treat canine urinary incontinence in some European countries. Its efficacy after 42 days of 2.0 mg/day treatment was 85% in a multicentric clinical trial performed on 129 bitches in 4 european countries. Hematological abnormalities are not observed when using dosages of 0.5-1.0 mg/day even for years, nor have they been reported in mid-term (3 months) chronic toxicity studies using 2.0, 6.0 and 10 mg doses. Vulvar swelling and male attractiveness is occasionally observed in bitches treated with estriol doses of >1.5 mg/day. Some signs of estrus can be observed in bitches administered higher dosages.

Unwanted pregnancy

Several estrogenic compounds have been used for this purpose, but for most of them the risk of side effects has discouraged their clinical application. Only estradiol benzoate, when given at low doses has proven to be fairly efficacious and relatively safe. A compound with estradiol benzoate is marketed for veterinary use in mismated bitches in several European countries, which is to be administered at the dose of 10 mcg/kg SC on day 3, 5 and 7 post breeding. No short-term side effects have been reported following this protocol. In a retrospective

study done in the UK the incidence of pyometra in the 4 months after the administration of low doses of estradiol benzoate was 8.7%, whereas the incidence of that condition in a practice situation was estimated to be < 2.0%.

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