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HOW I CONTROL REPRODUCTION IN DOGS

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INTRODUCTION

Medical control of reproductive cyclicity in dogs can be achieved using a variety of different drugs. Gonadal steroids such as progestogens and androgens have historically been used for a long time, and their action will be reviewed here. A recent development is the use of long acting GnRH agonists.

PROGESTOGENS

- Synthetic analogues of progesterone, also termed progestins or progestogens (PG), are pharmaceutical compounds commonly used to control the reproductive cycle of domestic animals. The following PGs are commonly used in dogs for temporary (starting the treatment shortly before proestrus onset) or prolonged (starting in anestrus) postponement of estrus, or for suppression of estrus (starting the treatment after proestrus onset): medroxyprogesterone acetate (MPA), megestrol acetate (MA), proligestone (PLG), chlormadinone acetate, delmadinone acetate, norethisterone acetate and melengestrol acetate. From the clinical point of view all these product act in the same way through a block of the production and/or release of GnRH from the hypothalamus. In theory these compounds may cause the display of a variety of side effects on the reproductive and endocrine system (such as hyperplasia of the endometrium, hyperplasia of the mammary parenchyma, decreased production of adrenocorticosteroids, increased secretion of prolactin and growth hormone, insulin resistance). However, it should be noted that the above effects are generally mild, often go unnoticed (being reversible when the treatment is discontinued) and are observed only when using a wrong protocol (too high dosage or too long administration) or when the treated bitch had a subclinical condition (cystic endometrial hyperplasia, microscopic mammary nodules, or subclinical diabetes) which is exacerbated by the progestogen. Side effects which are always observed regardless of the treatment protocol include local skin reactions at the injection site and behavioral modification (increased appetite and weight, polydipsia, slight depression, decreased libido in males). In pregnant bitches the use of PGs may cause masculinization of female fetuses if administered early in pregnancy (during organogenesis, up to day 25 after ovulation) or delayed parturition if administered in the last decade of pregnancy.

Clinical considerations for a safe use of progestogens - The above cited effects are not always present, are reversible and do not generally cause problems in healthy young to adult animals treated for not too long and using the recommended dosage. In general, a treatment period of 12 months is considered adequate in most individuals, although longer treatments (up to 18 months) can also be safe provided that the female is young and healthy. While most bitches and queens may tolerate treatment periods of more than 6 months, animals with a pre-existing disease such as subclinical diabetes, microscopic mammary lesion/tumor or cystic endometrial hyperplasia may see their condition worsen rapidly as a result of the PG treatment. The following is a series of considerations on patient selection and type of presenting complaint for which a PG treatment should or should not be used.

- Do not treat pregnant females, as this may cause fetal developmental defects as well as delayed parturition, thereby causing fetal death in utero due to placental ageing and detachment.
- Do not treat pseudopregnant bitches. During a PG treatment clinical signs of pseudopregnancy will disappear but will recur once treatment is discontinued, and the problem may worsen.
- Do not treat a female during diestrus. The stage of the reproductive cycle should always be identified using history, vaginal cytology and serum progesterone assay, and the bitch or queen should best be treated during anestrus. Diestrous should be ruled out in felines too, as approximately 30% of queens ovulate spontaneously, maintaining thereafter a 30-45 day-long diestrous.
- Do not treat females with uterine haemorrhage. Prolonged sanguineous vulvar discharge following parturition in the bitch can be a critical problem which should either be treated with a uterine contractive drug (i.e. as ergonovine) or sent to surgery. Milder bloody vulvar discharge can be caused by uterine neoplasia, cystic endometrial hyperplasia with superimposed endometrial inflammation, pyometra, metritis. None of these conditions will benefit from administration of a progestogen.
- Do not treat diabetic patients. Although not always necessary, it would be wise to measure blood glucose before and/or after a prolonged treatment to confirm health status with regard to glucose metabolism.
- Do not use PGs in females with prolonged heat. A prolonged heat may be due to ovarian cyst(s), a granulosa cell tumor, or a split heat (in the bitch) or to a misinterpretation of normal estrous signs by the owner. For none of these categories is a progestogen treatment indicated. Therefore, bitches or queens with a prolonged heat should not be treated with a progestogen, unless a diagnosis of cystic ovarian disease has been carefully confirmed and surgery or administration of GnRH or hCG are not a valid therapeutic option.

Choosing the right candidate - The ideal candidate is an adult, healthy postpuberal female in anestrus.

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Before a female gets treated with long acting compounds she should be evaluated for normality of uterine and mammary conditions as well as of glucose metabolism. In fact, a long acting progestogen might precipitate a subclinical uterine, endocrine or mammary condition (such as diabetes, cystic endometrial hyperplasia-pyometra in the bitch or mammary hyperplasia in the queen) which often are not clinically evident in the early stages, and which have been reported (albeit rarely) also in young animals. If one of the above conditions is present the administration of a long acting progestogen prior to diagnosis may pose a serious health threat to the female. A minimum database of clinical information to be gathered prior to administering a long-acting compound should include:

- collecting a thorough reproductive history to rule out occurrence of estrus within the last 1-2 months (which would mean that the female is in diestrus);
- a complete clinical exam;
- palpation of the mammary gland to rule out presence of mammary nodules;
- a vaginal smear to rule out presence of oestrus.

Table n° 1 shows the suggested dosages of the most commonly used progestogen-based compounds in the bitch.

<table>
<thead>
<tr>
<th>Suggested Dosage</th>
<th>Dog</th>
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<tbody>
<tr>
<td>Medroxyprogesterone Acetate</td>
<td>2.5-3.0 mg/kg IM every 5 months</td>
</tr>
<tr>
<td>Norgestimate Acetate</td>
<td>≤2.0 mg/kg administered for ≤2 weeks in proestrus, or ≤2.0 mg/kg administered for a longer duration of time in anestrus. A typical dosage for estrus suppression is 2.0 mg/kg/day for 8 consecutive days, while a typical dosage for temporary postponement is 0.5 mg/kg/day in late anestrus.</td>
</tr>
<tr>
<td>Progesterone</td>
<td>10-33 mg/kg SC every 2.4,5,6 months</td>
</tr>
</tbody>
</table>

Table n° 1 – Suggested dosages of the 3 most commonly used progestogen compounds in bitches for the control of estrous.

ANDROGENS

Androgens are also widely used for the control of the canine estrous cycle, although less information is available on most of the active principles commercially available for veterinary use. In the male, androgens cause a block of spermatogenesis (due to degeneration of seminiferous tubular epithelium), an increase in libido, a higher incidence of priapism, and growth of prostatic tumors. In the female, the main reproductive effect of androgens is to cause suppression of ovarian activity thanks to a negative feedback on the pituitary which decreases gonadotropin secretion; the ovaries of dogs treated with an androgen generally contain primary and secondary follicles but few that mature to ovulatory size. Androgens will also cause atrophy of mammary gland/endometrium and lactation arrest.

Mibolerone (originally marketed by Upjohn as Cheque drops) was until recently the only androgen approved for estrus suppression in bitches in the United States. Other androgens marketed in Europe for human or veterinary use such as testosterone, methyltestosterone nandrolone and stanazolol are sometimes used in bitches, although recommended dosages are not available for each one of these compounds. Androgens are not recommended for use in breeding animals. Estrus suppression can be achieved starting the treatment at least 30 days before onset of the next proestrus and for as long as estrus suppression is desired. Prolonged postponement can be achieved for 2-5 years. Return to estrus averages about 70 days, with a range of 7 to 200 days. There are no published reports describing fertility after treatment with androgens. Although most bitches seem to exhibit apparently normal fertility, cases of prolonged anestrus in bitches treated with androgens have occasionally been observed.

The most commonly reported side-effect of androgens in female dogs is clitoral hypertrophy, which occurs to some degree in 15 to 20% of dogs treated with mibolerone. Other reported side-effects of androgens include creamy vaginal discharge, vaginitis, increased mounting and aggressive behaviour, anal gland inspissations, musky body odor, obesity, and epiphora. Androgens are contraindicated in potentially pregnant bitches, as they may cause masculinization of female fetuses; in prepuberal bitches, in which they may precipitate premature phallic closure, and in dogs with renal or hepatic diseases. Presence of intranuclear hyaline bodies in hepatic cells and, rarely, changes in liver function tests have been described in dogs after treatment with mibolerone; clinical significance of hepatocellular changes is unknown.

Testosterone also has been described for estrus suppression in bitches. Successful regimens reported include injection of 100 mg testosterone propionate once weekly, oral treatment with 25 to 50 mg methyltestosterone twice weekly, and subcutaneous implantation of at least 759 g/kg. Testosterone, methyltestosterone and nandrolone are currently used with indications such as oestrus suppression, false pregnancy, lack of libido as well as with other non-reproductive indications (renal insufficiency, anemia, post-surgery etc.). Testosterone propionate (100 mg once weekly) and methyltestosterone (25-50 mg twice weekly per os) are currently marketed in some European countries for oestrus suppression. Canine false pregnancy can safely be treated with androgens as it does not recur following cessation of treatment unlike
LONG-ACTING GnRH AGONISTS

A recent development in the field of the control of reproduction in the bitch is the use of long-acting GnRH agonists such as deslorelin, which have become commercially available as veterinary drugs in Europe during 2008. In a recent study (Romagnoli et al., 2009) to evaluate clinical efficacy of deslorelin for inhibiting reproduction in the bitch, 10 adult, healthy bitches or bitches with mammary neoplasia for which owners were requesting suppression of cyclicity without performing gonadectomy were administered a 4.7 mg or a 9.4 mg deslorelin implant subcutaneously. The study design included history, physical exam, uterine ultrasound, haematology, serum biochemistry and progesterone (P4) assay to be performed prior to treatment, with physical exam and serum P4 to be repeated every 2.5 months until the treatment was discontinued. The first implant of deslorelin was administered in anestrus (N=5) or in diestrus (N=5). Treatment was repeated every 5 months for as long as necessary based on the clinical situation of the dog and owner's desires. Some of the bitches implanted in anestrus came in heat within 4-15 days after treatment, while none of the bitches implanted in diestrus showed heat during treatment. Suppression of reproductive cyclicity was successfully achieved in 6/10 bitches for 1-4 years. No behavioural and local/general side effect were observed in any of the treated bitches. The 4.7 mg deslorelin implant may work well for suppression of cyclicity provided that it is administered in diestrus and at intervals of 4.5 months. The 9.4 mg implant may be more suitable for this use although its efficacy may also be shorter than 12 months. Owner compliance is an important limiting factor.

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