ACC&D
Alliance for Contraception in CATS & DOGS

PROGESTINS

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Product Profile and Position Paper

A number of different synthetic progestational drugs have been used for temporary suppression of reproduction in dogs and cats, and these compounds have been extensively studied. Their effectiveness is based on interference in reproduction by both local actions in the reproductive tract, as well as effects on the brain, caused by negative feedback on GnRH release from the hypothalamus. These drugs come in both oral and injectable forms and have a variety of side effects, including suppression of immune function, diabetes, mammary tumor promotion and pyometra. The side effect profiles are related to the type of progestational drug used, when during the estrous cycle they are given, and the dose and the duration of use. Male and female cats and dogs each have unique responses to these drugs. Therefore, although in many cases effective for use in short term contraception, the risks and benefits of use in each clinical situation must be carefully evaluated, and veterinary oversight of use is essential.

Progestins

INTRODUCTION

Progestins, synthetic analogs of progesterone, have been used in domestic dogs and cats to control aspects of reproduction for decades. In fact, dogs were used as a model for humans to test steroid hormone contraception until it was recognized that mammary and uterine tissue of dogs did not respond to those hormones in the same way as humans (Finkel et al. 1973, El Etreby et al. 1979, Moyer and Felix 1998). However, the results of that research provide valuable information regarding the potential use of steroid hormones, such as progestins, as contraceptives in dogs. Later studies have focused on veterinary use of progestin-based contraceptives in cats and dogs, either in the clinic or for population control of free-ranging animals (e.g., Greenberg et al. 2013, Romagnoli 2015).

PRODUCT DESCRIPTION

Of the numerous progestins that have been synthesized, megestrol acetate (MA), medroxyprogesterone acetate (MPA), and proligestone (PROL) have been used most in dogs and cats. Synthetic formulations generally have greater potency and longer duration of action than natural progesterone. They also differ in how strongly they bind to receptors for progesterone and other steroid hormones, for example androgens and glucocorticoids (Duncan et al. 1963, Fekete and Szeberenyi 1965, Kloosterboer et al. 1988). Those characteristics determine their efficacy as contraceptives, as well as their potential side effects (Sloan and Oliver 1975; Selman et al. 1997). For example, those with strong binding affinity for androgen receptors can cause masculinizing effects (Grumbach et al. 1959, Wilkins 1960), and those binding glucocorticoid receptors can disrupt glucose activity and suppress immune function (Middleton et al. 1987, Huijbregts 2014).

The various progestin-based contraceptive products are commercially available as pills for oral administration and as slow-release depot-injections. However, not all products are commercially available in all countries, and they may have different brand names in different regions of the world.

MECHANISMS OF ACTION

Synthetic progestins have been shown to have anti-fertility effects at several points of the reproductive process. These include impeding the progression of sperm and eggs to the site of fertilization and interfering with embryo implantation. Progestins also have a negative feedback effect on areas of the hypothalamus and pituitary involved in reproduction (Diczfalusy 1968, Attardi 1984, Croxatto et al. 1982, Brache et al. 1985).

By suppressing the hypothalamic-pituitary-gonadal axis, progestins prevent the hormonal cascade that stimulates estrus and ovulation in females and spermatogenesis and libido in males. Progestin treatment of females can block ovulation by suppressing luteinizing hormone (LH) release from the pituitary, but levels of follicle-stimulating hormone (FSH) may remain high (Beijerink et al. 2007), which can stimulate follicle growth and estradiol production. Characteristics stimulated by estradiol, such as estrous behavior (heat), may continue despite adequate contraceptive efficacy. Progestin interference with LH production in

males can suppress testosterone, but very high doses are required compared to doses that are effective in females, which can exacerbate progestin-related side effects on the immune system. Because progestins can also affect sexual behavior, they are sometimes used to decrease urine spraying, roaming, and mounting in male dogs and cats (Hart 1980, Knol and Egberink-Alink 1989).

PROGESTINS: EFFICACY AND SIDE EFFECTS

Progestins also have common side effects, some potentially life-threatening, in carnivores, including domestic dogs and cats. Increased appetite and weight gain are common across species (Romatowski 1989). Progestins also have been associated with lethargy, hair loss, and hair discoloration (Evan and Sutton 1989). Progestin treatment in dogs and cats is commonly associated with uterine and mammary gland proliferation, especially when used at higher doses (Kutzler and Wood 2006, Romagnoli 2015). This proliferation can progress to development of mammary tumors and increase the risk of a potentially fatal uterine infection (pyometra). Progestins also can cause suppression of the immune system and changes in glucose metabolism that induce diabetes. Side effect profiles of specific progestins are given below.

Megestrol Acetate (MA)

Commercially available in pill form for oral delivery, megestrol acetate is currently available in Europe as Ovarid® (Virbac). MA is approved in the U.S. for managing reproduction in dogs but not cats. The original brand Ovaban® was produced by Intervet/Schering-Plough and is no longer available, but generic MA is available from compounding pharmacies. The MA product Megace® (Bristol-Myers Squibb) is marketed for humans in the U.S. and is sometimes used off-label for other species.

Although MA has not been approved by the FDA for use in cats, it has been used extensively in cats, in particular in Europe where Ovarid is approved for postponement or prevention of estrus in cats as well as dogs. MA was previously available in the U.S. as the compounded product FeralStat®, specifically for preventing reproduction in feral cat colonies, but is no longer available.

As the shortest acting progestin currently available for veterinary application, MA must be given at least weekly, although some dosing regimens call for a daily administration.

MA has both anti-androgenic and anti-estrogenic effects. In addition, as a cortisol agonist, MA can suppress the immune system, a function that has made it useful in treating some dermatologic conditions in cats (Middleton et al. 1987). However, if not carefully monitored, this immune suppression can result in susceptibility to infection.

Medroxyprogesterone Acetate (MPA)

Injectable Depo-Provera® (Pfizer), the most commonly used formulation of MPA, has a relatively long duration of action, with recommended re-injection every 4–6 months (Shille and Stabenfeldt 1980, Concannon 2004). It is available commercially around the world as a contraceptive for women. However, human studies show MPA to have the disadvantage among the progestins of being one of the most androgenic (Labrie et al. 1987) and having the strongest suppressive effect on the immune system (Hapgood et al. 2004, Huijbregts et al. 2014).

(MPA) is given to female dogs or cats by injection, usually every 5–6 months during anestrus, or in oral tablet form once per day. If the precise dose is calculated on a weight basis, side effects are minimized (Bryan 1973; Jöchle, personal communication). The label directions indicate that the tablets should not be

administered for more than two consecutive treatments, making this an impractical long-term solution for contraception.

Proligestone (PROL)

Another injectable progestin, proligestone, is approved for contraception in dogs and cats in Europe as Delvosteron®. Recommended dosing intervals vary, but one injection every 4–5 months is a common recommendation (Romagnoli and Concannon 2003). Research has shown the effects of PROL on reproduction to be primarily anti-gonadotrophic, that is, blocking ovulation, and less progestogenic than other synthetic progestins. Thus, effective contraceptive doses of PROL may be less likely to cause the side effects that are seen with other synthetic progestins that have more potent progesterone-like actions on mammary and uterine tissue (Van Os and Oldenkamp 1978, Evans and Sutton 1989). In a study of 160 female dogs, deleterious effects were detected in uterine and mammary tissue of those treated with PROL, but at lower percentages than in those treated with MPA (Parez and Sutton 1993). However, PROL has been shown to affect adrenal function, which can disrupt glucose homeostasis and cause immunosuppression (Selman et al. 1994a, 1994b). That adrenal effect, though, was found to be less severe than that caused by MA (Church et al. 1994).

DOGS

Use in Female Dogs

Progestin-based contraceptives have been used in female dogs for many years with mixed results. They are in general effective for short-term suppression of fertility, but most products and dosing regimens are accompanied by potentially serious side effects such as uterine and mammary tumors, as well as diabetes mellitus and acromegaly (excessive production of growth hormone by the pituitary gland).

Uterine pathology in female dogs

An association between Depo-Provera® (MPA) treatment and uterine pathology was first described in 1966 (Brodey and Fidler 1966). The findings were corroborated and extended to other progestins, such as MA, in many studies (e.g., Withers and Whitney 1967, Nelson and Kelly 1976, Von Berky and Townsend 1993). The pathology caused by progestins includes hyperstimulation of the endometrium, called cystic endometrial hyperplasia (CEH), which can be a precursor condition for pyometra, a potentially fatal uterine infection (Dow 1958, Noakes et al. 2001). The effect of progestins on endometrial growth was found to be exacerbated if the uterus had been sensitized by estrogen, either endogenous (as during proestrus) or exogenous administration (Dow 1958, Noakes et al. 2001). Thus, if progestin contraception of dogs is considered, treatment should not be initiated when estradiol has been elevated, as during proestrus. Protocols have been developed (see, e.g., Evans and Sutton 1989, Jöchle 1991) in which treatment with a low dose of progestin, such as Depo-Provera, is begun during deep anestrus when a female dog's endogenous estradiol is minimal. Treatment with PROL is considered less likely to result in uterine abnormalities (Van Os and Oldenkamp 1978, Parez and Sutton 1993).

Mammary tumors in female dogs

Progestin-based contraceptive products have also been found to stimulate tumor growth in mammary tissue of dogs (Nelson and Kelly 1976, Frank et al. 1979, Misdorf 1991). In contrast to other progestins, treatment with PROL was not associated with increased incidence of mammary tumors (Van Os et al. 1981). This difference may be due to the observation that PROL is more effective at suppressing

gonadotropin secretion than acting as a progestin. In addition, at least some progestins stimulate the production of growth hormone (GH) and possibly insulin-like growth factor (IGF-1) in the mammary glands of both dogs and cats (Selman et al. 1994c, Mol et al. 1996). Furthermore, tumor prevalence can simply be a function of dose; high but not low doses are more likely to result in mammary tumors, including carcinomas (Misdorp 1991).

Other side effects in female dogs

Of further concern is that GH release stimulated by progestins can contribute to development of diabetes mellitus (Nelson and Kelly 1976, Sönksen et al. 1993, Selman et al. 1994a). Treatment with progesterone or MPA (Eigenmann and Rijnberk 1981, Eigenmann et al. 1983) resulted in increased GH and altered glucose homeostasis, and MPA caused glucose intolerance (Rijnberk and Mol 1997). Although PROL appears to pose less risk to uterine and mammary tissue of dogs, it has a high affinity for the glucocorticoid receptor and can affect GH and the adrenal gland, both of which influence glucocorticoid dynamics (Selman et al. 1996, 1997). High doses of MPA also have resulted in acromegaly, a condition due to chronically high GH concentrations that cause abnormal growth of head, paws and internal organs, as well as skin thickening and folding (Concannon et al. 1980).

A further complication of progestin effects on the adrenal gland involves suppression of the immune response (El Etreby and Fath El Bab 1978). This effect can extend well beyond the treatment period (Selman et al. 1994), potentially compromising the ability of the animal to respond to infection. MPA and MA were shown to have equal potency in suppressing the adrenal gland (Briggs and Briggs 1973).

Although MPA and other progestins can stimulate GH production implicated in mammary tumor growth and glucose intolerance, there is no evidence that GH is an intermediary in development of endometrial pathology (Kooistra et al. 1997, Bhatti et al. 2007). Progestins have not been found to alter prolactin secretion, but minor effects on thyroid stimulating hormone (TSH) have been noted (Beijerink et al. 2007). Although some progestins have been shown to masculinize developing fetuses (Grumbach et al. 1959), a study of pregnant dogs treated with MA did not find masculinized features in female fetuses (David et al. 1963).

Potentially safe treatment protocols in female dogs

Although progestins have been shown to have numerous side effects in bitches, most studies have used relatively high doses. That, plus the observation that progestin effects are made worse when coupled with estrogen, as would happen if treatment began during proestrus or estrus, prompted development of protocols that should be safer. In particular, initiating treatment during deep anestrus and using a lower dose may avoid serious side effects (Jöchle 1974, 1991). PROL might also be considered, given the possible lower incidence of side effects than with the other progestins.

Use in Male Dogs

Progestins have been used in attempts to reduce sexual behaviors (e.g., mounting) potentially supported by testosterone (Joby et al. 1984, Knol and Egberink-Alink 1989), as well as for contraception (Wright et al. 1979, England 1997). Although behavioral changes can be more challenging to quantify, and there is no hard evidence to link suppression of testosterone to reduction in aggressive behavior, progestins have been more successful when used for suppression of sexual behaviors than for sufficiently suppressing spermatogenesis to assure contraceptive efficacy. A high dose of MPA did rapidly reduce sperm motility and numbers (England 1997), but whether infertility could be safely sustained at that dose is questionable.

Use in Pre-Pubertal Dogs

There is insufficient published information to determine if treatment before puberty would be more effective in achieving sterilization in male and/or female dogs. Results from studies of male dogs treated with progestins to reduce undesirable male-type behavior indicate that treatment before puberty, that is, before learned behavior patterns are established, is more effective (Knol and Egberink-Alink 1989).

CATS

Both MA and MPA have been used in cats to postpone estrus or prevent reproduction in females, as well as to reduce undesirable behaviors such as urine-marking and roaming in males. As with dogs, serious side effects have been documented, with the primary difference that progestin-caused uterine pathology has been reported less frequently in cats.

Use in Female Cats

Although progestins are in general very effective in suppressing reproduction at appropriate doses, side effects have often been reported. The range of side effects has been similar to those detected in dogs, although the likelihood of uterine pathology appears to be lower in cats (Romagnoli 2015).

Mammary tumors in female cats

Hernandez and colleagues were the first to report a link between a progestin (MPA) and mammary tumors in cats (Hernandez et al. 1975). This report was followed by others (e.g., Hinton and Gaskell 1977, Oen 1977, Hayden et al. 1981,1989), raising concerns about the suitability of synthetic progestins as contraceptives for cats. Although there is less evidence for a link to growth hormone and mammary tumors in cats compared to evidence in dogs, both MA and PROL have been found to stimulate GH release in cats as well as dogs (Mol et al. 1996).

Other side effects in female cats

MA, in particular, can decrease the activity of the adrenal gland, which can result in suppression of the immune response (Chastain et al. 1981, Middleton et al. 1987). In studies that directly compared MA and PROL, adrenal suppression, in particular, effects on glucose, was more pronounced in cats treated with MA (Watson et al. 1989, Church et al. 1994). MA has also been reported to induce diabetes mellitus (Mansfield et al. 1986, Middleton and Watson 1985, Middleton 1986, Peterson 1987). Similar to effects on the adrenal gland, MA but not PROL caused significant changes in insulin concentrations (Church et al. 1994), suggesting that PROL could be a safer alternative, at least when considering effects on glucose metabolism.

An important observation is that in studies of MA with adequate follow up, effects on the adrenal gland and on insulin levels were reported to regress when treatment was discontinued (e.g., Houdeshell and Hennessey 1977, review by Romagnoli 2015). In addition, in an early study with MPA, previously treated females were subsequently allowed to breed. Although kittens in first litters post-treatment were small, weak or even stillborn, subsequent litters were normal, demonstrating eventual complete reversal of the contraceptive effect (Harris and Wolchuk 1963). Behavioral effects, such as listlessness, docility and changes in general temperament, have occasionally been reported for cats treated with MA (Houdeshell and Hennessey 1977, Remfry 1978).

Potentially safe treatment protocols in female cats

As with dogs, questions have been raised about conclusions drawn from the various studies because of the differing and often very high doses of progestins used. In a comprehensive review of the literature on progestins used as contraceptives in cats, Romagnoli (2015) found that side effects were almost exclusively associated with relatively high doses. Even at doses he classified as intermediate, side effects that did occur tended to be temporary, especially for oral MA, which is much shorter acting than injectable MPA, which is formulated to be released slowly. Nevertheless, he recommends that MA and MPA should always be used with caution, at the lowest possible dosages, to safely control reproduction in pet cats as well as in feral cat colonies. The recommended dose of FeralStat® (MA compounded with lactose powder for palatability), promoted for limiting reproduction in feral cat colonies in the U.S., was in the range considered safe by Romagnoli. (FeralStat is no longer available.) However, there are no published reports on the efficacy of that low dose. Treating feral cats with oral MA by putting it on food at weekly intervals poses challenges, including controlling the dose consumed by each individual, which can result in under or overdosing individual cats; the inability to monitor side effects in treated cats; and exposing non-target species and pets to the drug.

Use in Male Cats

Progestins have been used in male cats primarily to reduce objectionable sexual behaviors, such as urine marking. MPA and MA were both effective in decreasing spraying, but in only 48% of males (Hart 1980). Although progestin treatment of male cats has not been studied as extensively as treatment of females, mammary hypertrophy and adenocarcinomas also have been associated with exogenous progestins in males (Hayden et al. 1981, Jacobs et al. 2010).

Use in Pre-Pubertal Cats

A recent study in very young kittens suggests that early treatment may not affect long-term reproduction. Even a very high dose of MPA failed to disrupt uterine development sufficiently to cause infertility (Lopez Merlo et al. 2016). However, the treatment did seem to predispose the kitten to future uterine disease.

ACC&D POSITION

ACC&D recognizes that progestins may be an effective method for short-term contraception in carefully monitored female dogs and cats with veterinary oversight. The benefit of short-term suppression of fertility must be balanced against the risks of the variety of side effects caused by the use of progestins. ACC&D cannot recommend progestins for use in free-roaming, outdoor, and/or colony situations, or for long-term use in any situation. Any use of progestins for contraception needs to be monitored closely by a pet's caregiver and veterinarian.

DISCLAIMER

The Board of Directors, Scientific Advisory Board, and staff of ACC&D assume no responsibility for and make no warranty with respect to results that may be obtained from use of non-surgical technologies or products, and do not necessarily endorse such use. ACC&D shall not be liable to any person for any damages, or equivalencies, or by reason of any misstatement or error, negligent or otherwise obtained in this work.

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