Available online at www.sciencedirect.com
ScienceDirect
Theriogenology
Theriogenology 66 (2006) 1560–1567
www.journals.elsevierhealth.com/periodicals/the

Dopamine agonists, anti-progestins, anti-androgens, long-term-release GnRH agonists and anti-estrogens in canine reproduction: A review

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Abstract

Over the last 10 years, new drugs have been applied to canine reproduction, widening the spectrum of therapeutic possibilities for diseases that were previously surgically treated, and facilitating better control of the estrous cycle and fertility. Some are not approved for use in dogs; their use is experimental and further clinical trials are necessary. Dopamine agonists such as cabergoline, bromocriptine or metergoline are ergoderivative alkaloids that exert an anti-prolactinergic effect via stimulation of D_2 pituitary receptors or inhibition of central serotoninergic ones. Their main indication is suppression of lactation. Anti-prolactinergic compounds have also been successfully used for pregnancy termination and shortening of interestrous intervals. Anti-progestins, (e.g. mifepristone and aglepristone) are synthetic steroids that bind with high affinity to progesterone (P_4) receptors, preventing P_4 from exerting its biological effects. Anti-progestins have been indicated in P_4-dependent conditions, such as pregnancy termination, induction of parturition and the medical treatment of pyometra. Several groups of drugs have been described to have anti-androgenic properties through different mechanisms of action: progestins, receptor binding anti-androgens (e.g. flutamide), competitive enzyme inhibitors (e.g. finasteride), aromatase inhibitors, and GnRH agonists. Their main application is medical treatment of benign prostatic hyperplasia. Long-term release formulations of GnRH agonists (e.g. leuprolide or deslorelin acetate) postponed puberty and reversibly suppressed reproductive function in male and female dogs for periods exceeding 1 year. Anti-estrogens (e.g. clomiphene and tamoxifen citrate) are synthetic non-steroidal type I anti-estrogenic compounds that competitively block estrogen receptors with a combined antagonist-agonistic effect. In dogs, their action is more agonistic than antagonistic.

Keywords: Dopamine agonist; Anti-estrogen; Anti-progestin; Anti-androgen; Long-term-release GnRH agonist; Dog

1. Introduction

Over the last 10 years, new drugs have been applied to canine reproduction. They have expanded the spectrum of therapeutic possibilities for diseases that were previously surgically treated, and they permit better control of the estrous cycle and fertility in general. Due to differences in availability of these drugs in various countries, the frequency of application and the general knowledge of these compounds vary considerably among practitioners.

Although most of these drugs have already been used for years in other species, only few are widely marketed or approved for use in dogs. The aim of this article is to briefly review the main pharmacological properties, reported trials and possible indications of new groups of drugs, e.g. dopamine agonists, anti-progestins, anti-estrogens, anti-androgens, and long-term-release preparations of gonadotrophin releasing hormone (GnRH) agonists for use in canine reproduction. Several of the

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doi:10.1016/j.theriogenology.2006.02.005

drugs discussed are not approved for use in dogs and/or as described; such use should be considered experimental, with the owner required to sign a release form where applicable.

2. Dopamine agonists

Dopaminergic agonists are ergotine-derivative alkaloid compounds that exert an anti-prolactinergic effect. Two of the most widely used dopamine agonists in dogs are bromocriptine and cabergoline, which have a direct action on D_2-dopamine receptors of the lactotrophic cells of the anterior pituitary gland. Metergoline, another ergot alkaloid, is a serotonin antagonist, exerting dopaminergic effects at high doses [1,2]. The ability of dopamine agonists to inhibit prolactin (PRL) secretion makes them optimal for milk suppression, either during overt pseudopregnancy episodes or in the post-partum period [3–7] and they are marketed with that indication in several countries. It is well known that PRL is a required luteotropic hormone during the second half of canine luteal phase [8]. Therefore, anti-prolactins can also be used to suppress luteal function in progesterone (P_4) dependent conditions such as pyometra, unwanted pregnancy [9–11] and mammary tumors.

Different combinations of either natural or synthetic prostaglandins (PG) F2α and dopamine agonists have been reported to efficiently terminate gestation from 25 days after the luteinizing hormone (LH) surge, without substantial side effects [12–14]. This drug combination was also used for medical treatment of various stages of spontaneous pyometra, with a success rate of 82% [15]. Dopamine agonists (e.g. cabergoline, 5 μg/kg/day po) have also been recommended for pre-surgery treatment of canine mammary tumors, and for reducing the incidence of mammary tumors by treating overt pseudopregnancy (associated with mammary tumors [16]), as well as for reducing mammary size before mammectomy [17]. Finally, treatment with PRL inhibitors shortened the interestrous intervals in bitches, either by advancing luteal regression or by reducing the anestrus period [7,18–20]. Although they were effective in inducing estrus in bitches with prolonged anestrus [21,22], precise mechanisms of action of dopamine agonists leading to estrus induction in anestrus bitches are not well understood. As estrous induction by dopamine agonists does not depend on decreasing serum PRL concentrations [7,23], perhaps they directly stimulate the hypothalamic-pituitary axis or exert a peripheral action on the ovaries.

In an early report, bromocriptine was used in four bitches (20 μg/kg bid po) from 1 to 5 days after the LH surge to the beginning of the next proestrus. The interestrous interval was significantly reduced in treated versus control bitches (123 ± 23 versus 245 ± 8 days, respectively) [18]. A pregnancy rate of more than 60% was reported [24] in bitches that were mated during bromocriptine-induced estrus. In an early study, using metergoline (12.5 mg im per bitch every 3 days, starting between 78 and 161 days after proestrus) the interestrous interval was significantly shorter than in the control group (144 versus 207 days, respectively). Ten treated bitches in this protocol ovulated and nine became pregnant, although the high dose of metergoline (1 mg/kg) provoked vomiting [25]. In another trial, metergoline (0.1 mg/kg bid po) administered to seven bitches 100 days after ovulation significantly decreased serum PRL concentrations, but did not affect the interestrous interval [26].

Oral treatment with cabergoline (5 μg/kg/day po) in bitches with prolonged anestrus resulted in estrous induction after 5–18 days of treatment and in pregnancy in all 28 bitches that were treated. [21]. Administration of the same dose of cabergoline from 30 days after the LH surge reduced the interestrous intervals from 216 to 66.5 days. However, none of these bitches became pregnant, probably due to insufficient uterine endometrial regeneration. Nevertheless, this study demonstrated that estrus cannot only be induced in anestrus, but also in diestrus [19]. The duration of cabergoline treatment was shorter in late versus early anestrus (means, 6 versus 20 days, respectively) and normal hormonal characteristics and fertility were obtained on induced cycles [20].

3. Anti-progestins

Anti-progestins are synthetic steroids that bind with great affinity to P_4 receptors, preventing P_4 from exerting its biological effects [27]. Some anti-progestins also have the ability to interact with different binding affinity for glucocorticoid receptors [27]. In dogs, the anti-progestins mifepristone (RU 486) and aglepristone (RU 534) have been used for experimental and clinical purposes, including pregnancy termination and management of pyometra. Aglepristone is available in the veterinary market of some American and European countries, with an indication for pregnancy termination. Aglepristone acts as a true P_4 antagonist at the uterine level, without initially decreasing serum P_4 concentrations. Mifepristone also terminated pregnancy in the bitch within 3–4 days, without side effects [28,29].