ABSTRACTS

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Pharmacodynamics and pharmacokinetics of a sustained-release implant of deslorelin in companion animals

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Gonadotrophin Releasing Hormone (GnRH) controls the release of the gonadotrophins Luteinising Hormone (LH) and Follicle-Stimulating Hormone (FSH) by the pituitary gland. When administered acutely, GnRH analogues stimulate the release of pituitary gonadotrophins. However, a chronic systemic dose decreases the synthesis and secretion of LH and FSH.

[D-Trp-6, Des-Gly] GnRH ethylamide, also known as deslorelin is a GnRH super-agonist (1). The amino acid sequence has been changed from the endogenous GnRH with two subsequent results:
• The new entity is less susceptible to enzymatic cleavage and therefore has increased potency,
• GnRH receptor (GnRH-R) binding affinity is much higher than that of endogenous GnRH.

Deslorelin is commercially available for dogs in a sustained release form provided by lipidic matrix based implants (Suprelorin 4.7mg and Suprelorin 9.4mg, Virbac SA, Carros, France).

PHARMACODYNAMICS: Hormones regulating the reproductive cycle are water soluble peptides that cannot cross the lipid bilayer of the cellular membrane. Their action on target cells is mediated via external receptors on the membrane. Binding of the hormone to these receptors is specific and based on a physical complementarity between the shape of the hormone and the receptors similar to the “key-lock” system.

Deslorelin binds to the GnRH-R and acts by suppressing the function of the pituitary-gonadal axis when applied in a low, continuous dose. In mammals, the GnRH-R is an atypical G protein-coupled receptor that does not express a cytoplasmic C-terminal tail (2). Consequently, the “desensitisation” seen with chronic low-dose exposure does not result from an internalisation of the receptor but rather from a post-receptor mechanism. The GnRH promotes selective activation or inactivation of specific intracellular processes. Genes involved in the synthesis of the gonadotrophins respond differently depending on whether the GnRH stimulation is intermittent or permanent, suggesting specific roles in the dual process of activation/desensitisation. Under the influence of a pulsatile release of GnRH, the GnRH-R activates second messengers that are responsible for the production of the LHβ- and FSHβ-subunits and for the α-subunit common to both LH and FSH.

During a sustained stimulation (with the deslorelin implant for example), a complex network of transduction pathways involved in gene expression is activated, resulting in an inhibition of the mRNA coding for the β-subunits of the gonadotrophins while increasing the free α-subunit levels in the serum. GnRH may also regulate the expression of its own receptor. In rats, a central suppression of FSHβ-subunits has recently been proven after use of a deslorelin implant in either intact male rats or in castrated male rats (3).

Finally, a parallel desensitisation of the Leydig cells to LH has been demonstrated in dogs (4).

PHARMACOKINETICS: Two specific studies have been performed to assess the pharmacokinetics of deslorelin, one in dogs and one in mice.

The mouse study established that deslorelin was released from a 4.7mg deslorelin implant at an average rate of approximately 20 μg/day, but slowed down considerably after 25 - 30 weeks in vivo. The slow release rate of deslorelin, and the dependence on diffusion and dissolution of the matrix for its release, allows the results of this study to be extrapolated to make conclusions about the release profile of deslorelin in dogs. The steady release rate of deslorelin, between approximately week four and week 25, in male mice correlates well with the expected efficacy in dogs of six months reduced plasma testosterone levels, after implantation.

A study in dogs used a radio-immunoassay (RIA) technique to measure plasma deslorelin levels and indicated peak levels of between 200 and 2,000 pg at about 14 days post-implantation (PI). From between days 20 and 30 PI, plasma deslorelin levels dropped considerably, until they dropped below the limit of quantification after about 80 days PI. Although more stable than GnRH itself, GnRH analogues are rapidly absorbed and rapidly eliminated, predominantly by metabolism to inactive peptide fragments, following parenteral administration. The mean elimination half-life of GnRH-agonists has been reported to be longer than GnRH itself (e.g. approximately 72 - 80 minutes for buserelin, regardless of the route of administration (5)). Despite its short half-life, the inclusion into a biocompatible lipid matrix (saturated triglycerides) provides a sustained release of deslorelin over time and allows for its long-lasting effect. Excretion is primarily via the urine.
CONCLUSION AND CLINICAL IMPLICATIONS: The features of the mammalian GnRH-R are responsible for the dual mode of action of sustained-release forms of GnRH-agonists. The first step of the mode of action is a “flare-up” effect with an increase of synthesis of gonadotrophins. This effect can be used to induce heat and ovulation in bitches for example. However, this increase may also be responsible for an exacerbation of clinical signs in animals that have been treated for hormonal disease (e.g. prostatic diseases, anal adenoma). The second step is related to the desensitisation of the GnRH-R with a suppression of synthesis of the gonadotrophins. This is the principal reason for clinical use of the GnRH agonists in companion animals (e.g. temporary infertility, treatment of benign prostatic hyperplasia, treatment of urinary incontinence (6)). The individual variations of the duration of action may be explained by the mode of action involving gene regulation.