Evaluation of etonogestrel, altrenogest and medroxyprogesterone bioactivity in mares using an in vitro bioassay

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Many mares fail to perform at their best due to strong sexual behavior and may become harder to manage, perform irregularly, or even appear painful when in heat. Because of performance problems associated with the estrus period in mares, several different progestins have been evaluated for efficacy in suppressing estrus in the mare. Currently no single treatment has been shown to be both effective and safe for prolonged estrus suppression. Etonogestrel (synthetic progestin currently used in implant form for long-term human contraception) showed some suppression of estrous behavior in a previous field trial using human doses (2 implants/mare, Dujovne, unpublished), suggesting that the determination of an effective dose for horses may provide a novel, long-acting, alternative therapy to safely suppress heat in mares.

Dose-response studies conducted in vivo are extremely expensive. Moreover, doses cannot be extrapolated from humans; if only based on the knowledge that the binding of various presumptive progestins to equine endometrial and mammary cytosolic extracts (source of progesterone receptor, PR) differs from extracts of human endometrium. Furthermore, binding is not a reliable indicator of PR activation, receptor antagonists are effective because of high affinity binding.

The following study was conducted to investigate the relative potencies of progesterone, etonogestrel, altrenogest and medroxyprogesterone acetate (MPA) as putative activators of the equine PR. An in vitro bioassay using Chinese hamster ovarian (CHO) cells expressing the equine PR was developed to test the relative bioactivity of various synthetic and natural progestins in horses (Scholtz et al, in press). Chinese hamster ovarian cells stably expressing the equine PR were transfected with a reporter plasmid expressing luciferase under the control of the progesterone-responsive mouse mammary tumor virus (MMTV) promoter. After 48 hrs, cells were exposed to progestins (0-1000nM) and luciferase activity was measured 24-36 hrs later.

Progesterone and altrenogest were equipotent and the most potent activators of the equine PR based on MMTV-induced luciferase expression. Almost no response was obtained with MPA even at the highest concentration tested. Etonogestrel was able to bioactivate the equine PR but at much higher concentrations than altrenogest. Therefore, the rank order of potency of these steroids as bioactive progestins in horses is predicted to be progesterone = altrenogest > etonogestrel >>> MPA.

We conclude that higher doses of etonogestrel are needed in horses than in women to induce a progestogenic response.

Keywords: Progestins, mare, estrus suppression, equine progesterone receptor, etonogestrel

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