Evaluation of BioRelease P4 LA 300 in the Mare

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Introduction

In addition to progestin treatment of non-cyclic recipient mares to induce cyclicity, progestin-treated non-cyclic mares are now frequently used as embryo recipients in large commercial programs. The practice is becoming particularly popular early in the year when cyclic recipients are frequently in short supply. Based on current research, only daily oral altrenogest (Hinrichs et al 1986; McKinnon et al 1988; 2000; Carnevale et al 2000), weekly altrenogest injection Morrow and Burns (2007) or progesterone injection in oil given every 24 to 48hours, or as once weekly long acting progesterone treatments (Ball et al 1992; Vanderwall et al 2003; Bringel et al 2003; 2004; Pessoa et al 2004) appear suitable for pregnancy maintenance in non-cyclic or ovariectomized recipient mares. The new once weekly controlled release formulations are advantageous in commercial programs because of the reduced labor and the associated handling stress to the animals and producers. Futhermore, such formulations offer veterinarians an important means of maintaining effective compliance rates on farms with wide varieties

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of management systems. The present studies were designed to evaluate the pharmodynamic properties of BioRelease P4 LA 300 a new biocompatible controlled release progesterone based product to better define the most appropriate dose of the formulation for pregnancy maintance and ovulation induction protocols in non cyclic mares. The BioRelease Delivery System is a proprietary low viscosity non-aqueous liquid system that uses an easily injectable biocompatible solution.

Experimental Methods

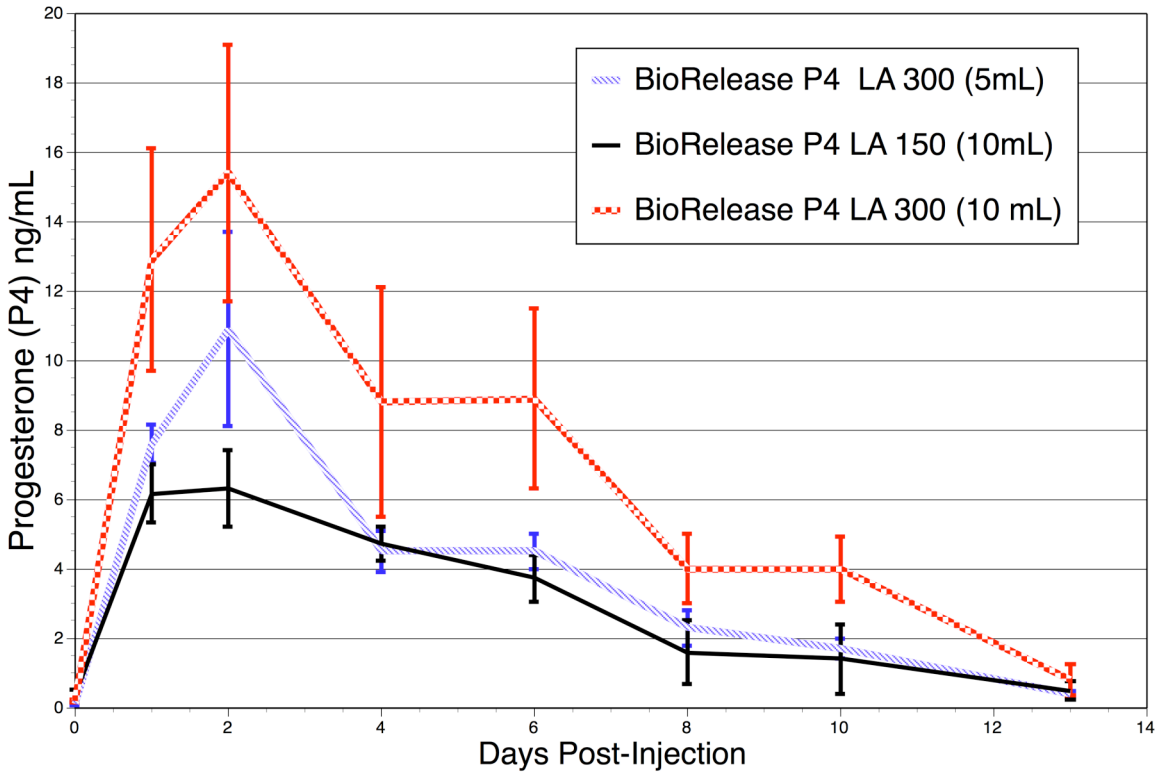
Study 1**:** In study 1, 18 non-cyclic anovulatory mares of various light horse breeds were assigned to one of 3 treatment groups (n=6 mares per group) , 5 mL (1500 mg) or 10 mL (3000 mg) of BioRelease P4 LA300 or 10 mL (1500mg) BioRelease P4 LA 150 (BET Pharm LLC, www.BETPHARM.com). Formulations were prepared to give a final concentration of 300 or 150 mg/mL, respectively and designed to deliver progesterone for approximately 10 to 12 days after I.M. injection using a 18 to 20 gauge needle. Beginning prior to injection (day 0) serial blood sample collections were initiated. Samples were collected on days 0, 1, 2, 4, 6, 8, 10, and 13 post-treatment. Serum was harvested and stored at -20ºC until assay for progesterone by RIA as described by Fay & Douglas, 1987.

Study2: In study 2, Sixty anovulatory recipient mares of various light horse breeds were assigned to one of 2 treatment groups (n=30 mares per group). The anovulatory mares were mares that had not responded to increased photoperiod (16 hours/day) in large outside pens (failure to obtain a follicle > 15mm after more than 50 days of lighting). Based on previous studies treated mares received 2 mL of BioRelease P4 LA300 as a IM injection and control mares received 2mL vehicle. Mares were evaluated at weekly

intervals by ultrasound for ovulation. Mares with uterine folds and large follicles (> 35mm) were treated with hCG to induce ovulation. The experimental endpoint evaluated was the percentage of mares ovulating within four weeks of treatment.

Results and Discussion

Study 1: Statistical examination of the data indicate significant treatment dose by day interaction ($p<.0.05$). Mares receiving 10 mL of BioRelease P4 LA 150 or 5mL of BioRelease P4 LA 300 had similar progesterone levels while mares receiving 10 mL BioRelease P4 LA 300 had higher P4 levels for the first10 day of the study. Serum progesterone concentrations are shown in the figure below. The results from the present study clearly demonstrate that 5 mL BioRelease P4 LA 300 provided elevated serum progesterone for 10 days similar to those observed after treatment with 10 mL of BioRelease P4 LA 150.



Furthermore, although not statistically evaluated, the investigators indicated the 5mL volume of the P4 LA 300 seemed to have slightly better biocompatibility than when 10 mLs of either P4 LA 300 or P4 LA 150 were injected.

Study 2: In this study, P4 LA 300 treatment was effective ($p<0.05$) at inducing ovulation in non-responding "lighted" mares that had been lighted >50 days but had follicles < 15mm prior to treatment. In this group, 57% (17/30) of the P4 LA 300 mares ovulated within 4 weeks following treatment compared to 7% (2/30) in control mares. Furthermore, continued clinical evaluation of P4 LA 300 (2mL) in hundreds of non-responding "lighted" mares or late transitional mares continues to be effective at establishing cyclicity and remains to be the treatment of choice for transitional recipient management (J. Abraham, Personal communication 2008).

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