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ORIGINAL ARTICLE

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Administration of progesterone BioRelease LA inhibits follicular growth in llamas (*Lama glama*) regardless of follicle diameter at the start of treatment

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Abstract

The aims of the study were twofold: first, the comparison of the pharmacokinetics parameters of two doses of Progesterone BioRelease® LA, (BioRelease Technologies, Lexington, KY, USA) one of 300 mg and other of 150 mg and their effects on ovarian dynamics in llamas. Based on the results from the first study, the aim of the second study was to evaluate the effect of the doses of 150 mg of progesterone on follicular activity considering the stage of the largest follicle at the beginning of treatment. The results in Study 1 showed that both doses of the formulation induced plasma progesterone concentrations higher than 1 ng/ml during the first 6 days of treatment in all females, progesterone concentrations steadily decline until Day 5 following by a slowly decrease. The total amount of progesterone released during treatment was higher in Group 300 than in Group 150 (p = 0.045). Mean maximum concentrations were 14.9 ± 2.24 and 14.3 ± 2.16 ng/ml for Group A versus Group B (p = 0.58), and they were registered on Day 1.5 ± 0.22 and 1.7 ± 0.34 days, respectively (p = 0.10). None of the animals of Group A showed progesterone concentration below 1 ng/ml during all studied period. The treatment applied in Study 2 was efficient in inhibiting the ovarian follicular dynamics and to start a superestimulatory treatment. The use of progesterone Biorelease® LA of 150 mg in comparison with the dose of 300 mg could be more effective in the use of synchronization protocols in llamas for AI or prior to the application of an ovarian superstimulatory treatment.

1 | INTRODUCTION

Over the last few years, an increasing interest in the production of meat and fibre in South American Camelids (SAC) has been developed in South America and around the world. The major limitation to further increase the rate of genetic improvement in SAC has been the poor reproductive rate and rather long generation interval of the species (Aller, Cancino, Rebuffi, & Alberio, 2010). Camelids present a long period of gestation (342–350 days) and only deliver one young per year, so the number of offspring a female may have is limited (Carretero, Miragaya, Chaves, Gambarotta, & Agüero, 2010). Therefore, it is of interest to apply biotechnologies such as artificial insemination (AI), ovarian superstimulation protocols and embryo transfer technique as alternatives to improve the reproductive efficiency in these species and reduce the generation interval.

Llamas are induced ovulators requiring copulation to trigger the ovulatory process (England, Foote, Matthews, Cardozo, & Riera, 1969; Fernández Baca, Madde, & Novoa, 1970; Novoa, 1970; San Martin et al., 1968). In nonmated females, ovarian activity occurs in waves of follicular growth and regression. The time required to complete a wave in llamas is between 22 and 24 days with a growing phase during the first 9–10 days, a plateau phase the next

5 days and a regression phase for the last 8–9 days (Cavilla, Bianchi, Maistruarena, & Aba, 2013; Chaves et al., 2002) and almost all follicular waves are superimposed on the preceding wave (Cavilla et al., 2013). Thus, unmated females remain almost with constant receptivity (England, Foote, Cardozo, Matthews, & Riera, 1971).

However, the ability to respond to an ovulatory stimulus depends on the stage of the follicular wave, with ovulation occurring only in the presence of a follicle ≥0.7 cm (Bravo, Stabenfeldt, Lasley, & Fowler, 1991). Besides, ovarian status at the time of superstimulatory treatment has been shown to influence the magnitude and variability of the follicular response in cattle (Adams, Ratto, Collins, & Bergfelt, 2009) and SAC (Bourke, Kyle, McEvoy, Young, & Adam, 1995; Miragaya, Chaves, & Agüero, 2006). To be able to start a superovulation protocol in the correct time or to ensure that mating or insemination coincides with the presence of a healthy, dominant follicle, it is necessary to develop an effective method to control follicular activity.

Several protocols have been design to control ovarian activity in SAC, from the manual ablation (Sansinena et al., 2007; Sansinena, Taylor, Taylor, Denniston, & Godke, 2003) or ultrasound-guided transvaginal aspiration of the dominant follicle (Berland et al., 2011; Ratto, Berland, & Adams, 2002; Ratto, Berland, Huanca, Singh, & Adams, 2005) to the use of the negative effect that progesterone has on follicular activity (Aba, Forsberg, Kindahl, Sumar, & Edqvist, 1995). The use of progesterone and progestogens is efficient in the inhibition of follicular growth in different species (Lauderdale & Zimbelman, 1974). In llamas, endogenous progesterone inhibits the follicular growth, reduces the size of the dominant follicle and shortens the duration of the follicular wave (Adams, Sumar, & Ginther, 1990). Daily injections of 50 mg of progesterone were evaluated over a period of 12 days showing a reduction in follicle diameter below 0.5 cm on Day 7 of treatment (Alberio & Aller, 1996). An intravaginal device CIDR®, containing 0.33 g of progesterone, was used in llamas for 16 days, reaching a rapid increase in plasma progesterone concentration, a peak was attained on Day 1 after insertion and, thereafter, concentrations decreased gradually (Chaves et al., 2002). In this study, a significant decrease in the number of follicles in late growing, plateau or regressing phase was observed while those follicles in early growing phase did not reach the dominant stage (Chaves et al., 2002). Cavilla, Bianchi, Aguilera, Hermida, and Aba (2016) compared two intravaginal devices (IVD) with two different concentrations of progesterone, one containing 780 mg and other containing 160 mg. It was shown that the IV devices containing 780 mg of progesterone suppressed follicular development and hastened the emergence of a new follicular wave in all females regardless of the follicular phase at the time of IVD insertion. Recently, long action injectable progesterone has been formulated. In equines, a formulation of progesterone BioRelease® LA (BioRelease Technologies, Lexington, KY, USA) USA has been shown to keep mean blood levels of progesterone above 2 ng/ml for approximately 10 days (Bingle, Jacob, Zimmerman, Alverenga, & Douglas, 2003). Achieving control of ovarian dynamics from the use of a simple protocol and with a single intramuscular application in the llama would be very useful to work with many animals at the same time to subsequently apply some of the reproductive biotechnological techniques.

Therefore, the aims of the study were twofold: first, the comparison of the pharmacokinetics parameters of two doses of Progesterone BioRelease® LA, one of 300 mg and other of 150 mg and their effects on ovarian dynamics in llamas. Based on the results from the first study, the aim of the second study was to evaluate the effect of the lower dose (150 mg) of progesterone on follicular activity considering the stage of the largest follicle at the beginning of treatment.

2 | MATERIALS AND METHODS

A total of 20 mature, nonpregnant, nonlacting female llamas (*Lama glama*), ranging between 5 and 10 years of age and with an average body weight of 100 ± 20 kg were used in this assay. All females were kept separated from the males, were in good nutritional status with a mean body condition score of 3 (body condition score, from 1 = emaciated to 5 = obese) (Edmonson, 1989) and fed with hay and water ad libitum.

The assay was conducted in the Faculty of Veterinary Sciences of the University of Buenos Aires, in Buenos Aires, Argentina, situated 34°36′S and 58°26′W, at sea level. The study was approved by the Institutional Committee for the Use and Care of Laboratory animals (CICUAL) of the Faculty of Veterinary Sciences of the University of Buenos Aires (Protocol No 2015/1).

2.1 | Study 1

Fourteen llamas were randomly selected and were assigned into two groups: A (n = 6) received a single dose of 300 mg and B (n = 8) a dose of 150 mg Progesterone BioRelease® LA (BioRelease Technologies) in the semitendinosus or semimembranosus muscle (Day 0). Follicular size was daily monitored with transrectal ultrasonography (Berger® LC 2010 plus attached to a 5.0 MHz linear-array electronic transducer, Buenos Aires, Argentina) every 24 hr for 10 days after treatment administration.

For the evaluation of plasma progesterone concentration, daily blood samples were collected by venipuncture in the jugular vein, alternating both sides of the neck, to prevent vascular damage. Blood samples were taken before the administration of progesterone (hour 0), and daily, until Day 10.

Blood samples were held in tubes with heparin and centrifuged immediately after collection, to recover the plasma, for 20 min at 1,008 *g*. Plasma was obtained with a Pasteur pipette and stored at −20°C in cold-resistant tubes (Polistor S.R.L). Plasma progesterone concentrations were measured by RIA kit (DPC, Los Angeles, CA, USA), previously validated for llama plasma (Bianchi, Meikle, Sartore, Gonzalez, & Aba, 2007). Pharmacokinetic parameters were determined, after a single intramuscular administration of 300 or 150 mg of progesterone BioRelease®, using noncompartmental analysis. The plasma concentrations versus time curves obtained after each treatment in each individual animal were fitted with the PK Solutions 2.0 (Ashland, Ohio, US) computer software. Pharmacokinetic

parameters were determined using a noncompartmental model method. The peak concentration (C_{max}) was read from the plotted concentration–time curve in each individual animal. The area under the concentration–time curves (AUC) were calculated by the trapezoidal rule (Gibaldi & Perrier, 1982) and further extrapolated to infinity by dividing the last experimental concentration by the terminal slope (lz). The sensitivity of the assay was 0.10 ng/ml, the intra-assay coefficient of variation was below 7% and the inter-assay coefficient of variation remained beneath 4% for concentrations between 0.10 and 40 ng/ml.

In Study 1, the different doses of progesterone were administered irrespective of the stage of ovarian follicular wave at the start of treatment. Based on the results of Study 1, the 150 mg dose was selected and used in Study 2.

2.2 | Study 2

Ovarian dynamics of fourteen llamas was assessed by transrectal palpation and transrectal ultrasonography, to determine the follicular phase of each female 2 days prior the assay. Females were classified randomly according to their ovarian follicular phase in four groups as previously described (Chaves et al., 2002):

- Group I: (n = 4) growth phase, with follicles <0.7 cm diameter.
- Group II: (n = 3) growth phase with dominant follicles (follicles of ≥ 0.7 cm diameter).
- Group III: (n = 3) Follicles in plateau phase (with variations in follicle diameter of ≤0.1 cm in two consecutive measurements).
- Group IV: (n = 4) follicles in regression (with two consecutive decreasing measurements).

The third ultrasonography, on which the phase of follicular wave was defined, was considered the Day 0 of the study and 150 mg of Progesterone BioRelease® LA (BioRelease Technologies) USA was injected in the semitendinosus or semimembranosus muscle in each female. Thereafter, transrectal ultrasonographies were performed daily and the diameter of the largest follicle was registered until Day 10.

2.3 | Statistical analyses

An ANOVA test was used in repeated samples to detect differences in the diameter of the largest follicle at the beginning and at the end of the study between Groups A (300 mg) and B (150 mg), and between the different phases of the follicular wave within Group B. The area under the concentration–time curve (AUC) from time zero to the last measurable concentration was calculated by the trapezoidal rule (Baggot, 1995). A Student's t test was performed to detect the differences between the pharmacokinetic parameters (C_{max}, T_{max}, and AUC). Statistical analyses were carried out using the Infostat software package (Córdoba, Argentina, 2011p). Statistical significance was set at $p < 0.05$. Data are expressed as mean ± *SEM*.

3 | RESULTS

3.1 | Study 1

Both doses of the formulation induced plasma progesterone concentrations higher than 1 ng/ml during the first 6 days of treatment in all females. An increase in plasma progesterone concentrations was observed after the injection of the formulation, with peak concentrations attained between Day 1 and 2. Thereafter, progesterone concentrations steadily decline until Day 5 following by a slowly decrease. The total amount of progesterone released during treatment was higher in Group 300 than in Group 150 registering AUC values of 67.3 ± 8.61 ng × day/ml and 47.1 ± 7.34 ng × day/ml for Groups A and B, respectively (p = 0.045). Mean maximum plasma progesterone concentrations were 14.9 ± 2.24 and 14.3 ± 2.16 ng/ml for Group A versus Group B (p = 0.58), and they were registered on day 1.5 ± 0.22 and 1.7 ± 0.34 days, respectively (p = 0.10).

By Day 8 post-treatment in 75% (six of eight) of the animals in Group B, plasma progesterone concentrations were below 1 ng/ml.

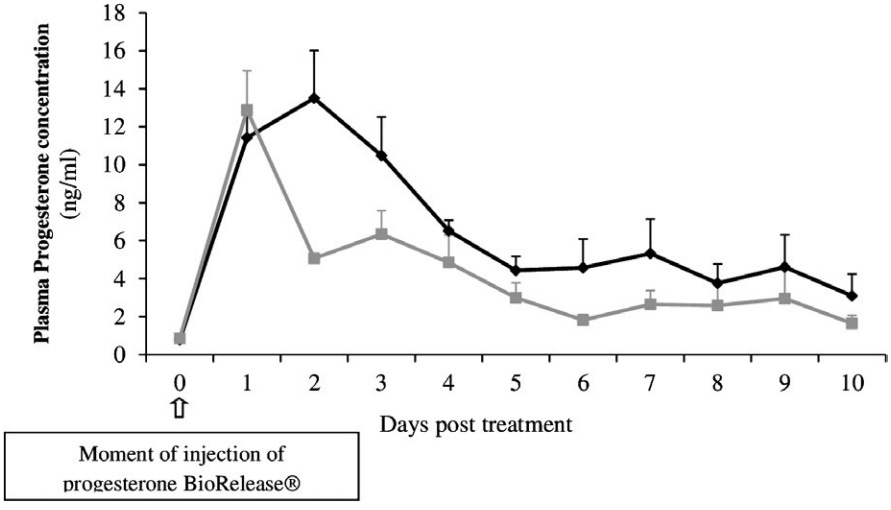

FIGURE 1 Plasma progesterone concentration (ng/ml) from the day of the injection (Day 0, arrow) of 300 mg (black line) and 150 mg (grey line) of Progesterone BioRelease® LA (Day 0) to the Day 10 after treatment

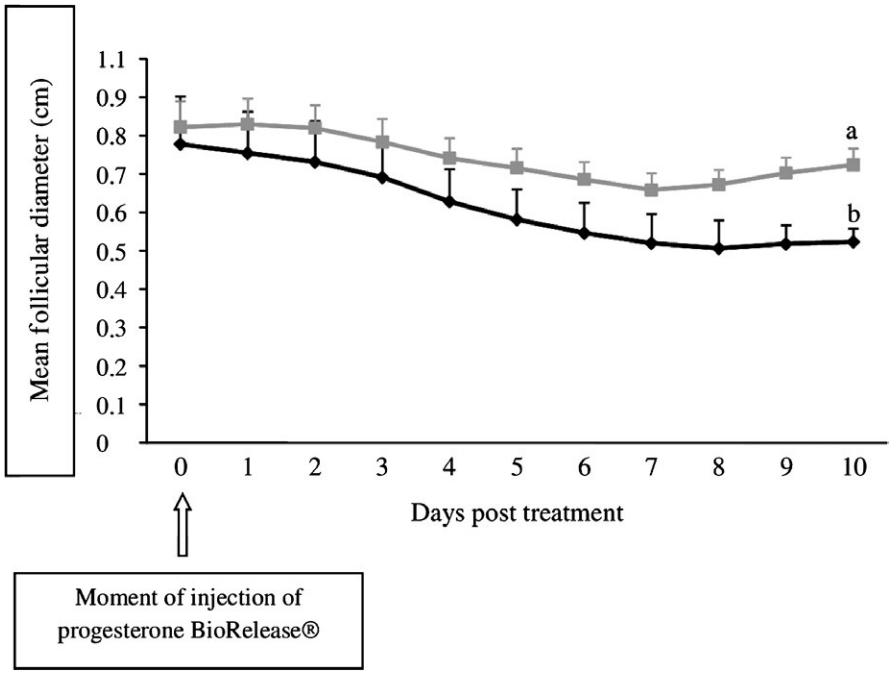

FIGURE 2 Mean follicular diameter (cm) from the day of the injection of 300 mg (black line) or 150 mg (grey line) of Progesterone BioRelease® LA (Day 0, arrow) and during 10 days. Different letters indicate significant differences ($p < 0.05$)

None of the animals of Group A showed progesterone concentration below 1 ng/ml during all study period (Figure 1).

No significant differences were registered in the average diameter of the largest follicle at the beginning of the treatment (0.78 ± 0.12 and 0.82 ± 0.07 cm in Groups A and B, respectively) ($p = 0.81$). At the end of the treatment, the average diameter of the largest follicle was smaller in Group A (0.52 ± 0.03 cm) compared to B (0.72 ± 0.04 cm) ($p = 0.01$). In Group B, 71% (10/14) of the females developed an ovulatory follicle (≥0.7 cm) at Day 10. In Group A, none of the animals had an ovulatory follicle by the end of the study (Figure 2).

3.2 | Study 2

Based on the results of Study 1, the lower dose was evaluated considering the stage of the follicular wave at the beginning of the treatment.

The average diameter of the largest follicle at the beginning of the treatment for each stage of the follicular wave was as follows: Group I: 0.56 ± 0.05 cm; Group II: 0.94 ± 0.10 cm; Group III: 1.11 ± 0.05 cm and Group IV: 0.78 ± 0.11 cm. The mean follicular diameter of the growth phase was significantly smaller than in the other phases ($p = 0.04$).

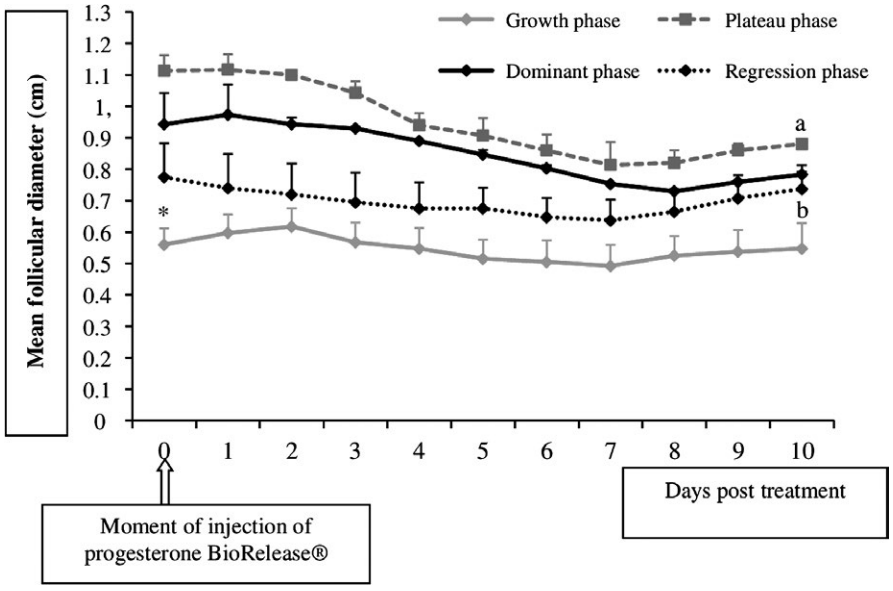

FIGURE 3 Mean follicular diameter (cm) from the day of the injection of 150 mg of Progesterone BioRelease® LA (Day 0, arrow) and during 10 days in the growth, dominant, plateau and regression phases. Asterisk means that differs significantly from the others ($p < 0.05$). Different letters indicate significant differences ($p < 0.05$)

During the treatment, the mean follicular diameter decreased from Day 0 to Day 7 in animals from Groups II, III and IV. In Group I (growth phase), follicle size remained steady during all the study, without further development of dominant follicles, except in one animal. The average diameter of the largest follicle at the end of the treatment was 0.55 ± 0.08; 0.78 ± 0.03; 0.88 ± 0.01 and 0.73 ± 0.05 cm for Group I, II, III and IV, respectively. The mean follicular diameter of the growth phase (Group I) differed significantly with the plateau phase (Group III) but not with the other phases ($p = 0.03$). Of all animals of dominant and plateau phase, 75% (three of four) animals in regression and only 25% (one of four) animals in growth phase had an ovulatory size follicle (≥0.7 cm) by Day 10 (Figure 3).

4 | DISCUSSION

It has been shown that progesterone from the corpus luteum and progestogens exert a negative influence on follicular activity in llamas (Aba, Quiroga, Auza, Forsberg, & Kindahl, 1999; Adams et al., 1990) and the results of the present work confirm this.

Progesterone BioRelease® LA was firstly used in horses, in which one dose of 1,500 mg maintained progesterone levels below 2 ng/ml (Bingle et al., 2003). In this work, the profile of plasma progesterone concentrations using the lower dose was similar to that previously reported in equine with a dose of 600 mg (Staempfli et al., 2011) and in llamas using an intravaginal progesterone-releasing device (Chaves et al., 2002). These last authors observed a rapid increase in plasma progesterone concentration immediately after the insertion of the CIDR® (Day 0), with a peak concentration on Day 1. The plasma concentration rapidly decreased until Day 3 of treatment and then decreased slowly, until reaching basal levels. Aller et al. (2015) obtained this same pattern of circulating progesterone using two different intravaginal devices containing the same dose (500 mg). Besides, the results of the present study showed that the treatment of 150 mg of Progesterone BioRelease® LA was more efficient in inhibiting the ovarian follicular dynamics and it was observed follicular growth by Day 7 and 8 and an ovulatory size follicle at the end of the treatment (Day 10). In llamas, with the injection of 300 mg of Progesterone BioRelease® LA, the plasma progesterone concentrations were still higher than 1.5 ng/ml until Day 10 and, by ultrasonography, follicles maintained their diameter below 0.8 cm indicating that progesterone affects negatively the follicular development. Similar observations were previously reported in llamas (Aba et al., 1999; Adams et al., 1990; Cavilla et al., 2016),and it has been suggested that progesterone treatments are effective in completely preventing follicular development for a period of up to 7 days (Chaves et al., 2002).

The observation in the Study 2 that progesterone inhibited follicular growth regardless of the stage of follicular development at the time of the injection indicates that the treatment could be used without previous ultrasonography exploration of the ovarian activity as previously reported with the use of intravaginal progesterone-releasing devices (Cavilla et al., 2016; Chaves et al., 2002).

The use of Progesterone BioRelease® LA of 150 mg in comparison with the dose of 300 mg is more effective in the use of synchronization protocols in llamas. The treatment applied in this study was effective in inhibiting the ovarian follicular dynamics. This injectable progesterone can be used as an alternative method to the generally used intravaginal devices which are presently unavailable in certain markets or as an alternative method of other injectable progestogens which are given several days; this progesterone is given only once, avoiding pain in the site of application and being less stressful to the animal.

5 | CONCLUSION

The Progesterone BioRelease® LA inhibits the follicular activity, so this treatment could be useful in synchronization protocols for AI or prior the application of an ovarian superestimulatory treatment when used at a dose of 150 mg.

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CONFLICT OF INTEREST

None of the authors have any conflict of interests to declare.

AUTHORS' CONTRIBUTIONS

M.Fernanda Veiga performed the study and wrote the manuscript. Virginia Trasorras participated in the performance and help with the extractions. Evangelina Moncalvo helped with the animals and extractions. Carolina Bianchi and Marcelo Aba helped in the design of the study and determine the hormonay essay. Graciela Chaves helped in designing the study and with the animals. Marcelo Miragaya designed the study and contributed with the manuscript.

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