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Effect of Administration of Different Progesterone Formulations on the Plasma Progesterone Concentrions in She-Camel

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Abstract: Administration of progesterone in form of intravaginal devices in she camel has produced a uniform plasma concentration of progesterone depending on the dose of the device. Subcutaneous implant and intramuscular injection of progesterone produced a non-uniform plasma concentration of the hormone, possibly because of the damage to injection site in the muscle as reflected in elevated plasma creatine kinase activity. This suggested that the intravaginal device administration maybe a better route to provide a constant concentrations of progesterone in camel.

Key words: Progesterone, intravaginal device, plasma, camel

INTRODUCTION

In dromedary camels, synchronization of follicular development and ovulation (Mckinnon *et al*., 1994) or preparation of recipients for embryo transfer without induction of ovulation (Scudamore *et al*., 1992) are among the indications for progesterone treatment. Methods of administration of progesterone include daily injections, pour-on formulation, oral consumption, intravaginal devices and subcutaneous implants (Thompson, 2001). Commercial preparations of progesterone designed primarily for use in cattle are currently being used in the camel without adequate pharmacokinetic information (Al-Busadah and Homeida, 2004). Usually, drug manufacturers give no specific recommendation for the camel so the doses used clinically in this species are, in general, extrapolated from other large domestic animals. This is not without danger because toxic effects sometime occur in camel given drugs at doses apparently harmless to other species (Al-Dughaym *et al*., 1998).

This study was conducted to determine the effects of administration of different pharmaceutical formulations of progesterone on plasma concentrations of progesterone in camels.

MATERIALS AND METHODS

Animals: Thirty five non-pregnant female camels aged 3-4 years and weighing 250-400 kg, selected on the basis of normal health and oestrous cyclicity were used for this study. They were fed daily with 2 kg of mixture of barely and wheat bran and hay and water were provided *ad libitum*.

A male camel was used to help detection of estrus. Progesterone was administrated on the day of estrus and thereafter.

Treatment groups: Animals were divided randomly into the following groups:

Group 1 (PRID group): Animals were treated with progesterone intravaginal device inserted into the vagina for 12 days. The PRID (Ceva, Southampton, UK) contained 1.55 g progesterone after removing the capsule of oestradial benzoate.

Group 2 (CIDR-B group): Animals were treated with controlled internal drug release dispenser (Smith Kline Beechanu, UK) inserted into the vagina for 12 days. The CIDR-B contained 1.90 g progesterone.

Group 3 (CIDR-S group): Animals were treated with CIDR-S inserted into the vagina for 12 days. CIDR-S contained 0.365 g progesterone per device.

Group 4 (veramix group): Animals received veramix sheep sponges (Upojon Ltd, Fleming Way, Sussex, England) Containing 60 mg 6-meth L-17-acetoxy- progesterone. Sponges were inserted into anterior vagina and removed after 12 days.

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Group 5 (sil-estrus implant group): Animals received a Subcutaneous (SC) implant of sil-estrus (Abbot. Laboratories, S.A., Athens Greece) containing 375 mg, progesterone in a silicone elastomer matrix.

Group 6 (i.m. progesterone group): Animals received an intramuscular (i.m.) injection of 10 mg progesterone (Sigma, UK) in sesame oil daily for 12 days.

Group 7 (control group): Animals were kept for 13 days as untreated controls. Blood samples were collected daily at 900 h by jugular venepuncture. Blood was collected into hepranized tubes. Plasma was separated and stored at -20°C until analysis.

Harmone and enzyme analysis: Progesterone concentrations were determined by radioimmunoassay as described previously (Homeida and Al-Eknah, 1992; Al-Busadah and Homeida, 2004). The sensitivity was 23.3 pg assay^{-1} tube, the intra-and interassay coefficients of variation were 5.2 and 12.1%, respectively.

Plasma Creatinekinase (CK), Aseparate Aminotransferase (AST), Alanine Aminotransferase (ALT) and Lactate Dehydrogenase (LDH) were determined in an autoanalyser (Hitachi, Japan) using specific kits (Randox Laboratories Ltd, Crumlin, North Ireland).

Statistical analysis: Treatment effects on the mean plasma progesterone concentrations were compared using student tiest.

RESULTS

Progesterone concentration in the peripheral plasma following administration of different pharmaceutical formulations of progesterone are given in Fig. 1. All formulations have significantly ($p<0.01$) produced increased concentration of progesterone in plasma of camels for 12 days. The plasma progesterone concentrations were approximately 2 fold higher in camels receiving PRID and CIDR-B than in those receiving CIDR-S and Veramix. CIDR-S gave a significantly ($p<0.01$) higher release of progesterone in plasma than Veramix. Subcutaneous implant and intramuscular administration produced inconsistent concentration of progesterone in plasma. Both routes of administration produced significant increase in creatine kinase activity from pretreatment sample of 55.1±13.6 U L^{-1} to a range of 160-210 U L^{-1} in case of SC implant and i.m. injection between 1 and 3 days after progesterone administration. Values of the enzyme returned to 62±25 U L^{-1} after 5 days in SC implant group and to 71±22 U L^{-1} after 7 days in the i.m., group. Values of the enzyme were in the range of 59-63 U L^{-1} in the intravaginal and control groups. The AST was in the range of 61.2- 63.1, ALT 32.1-34.1 and LD 296-300 U L^{-1} in control and progesterone treated animals.

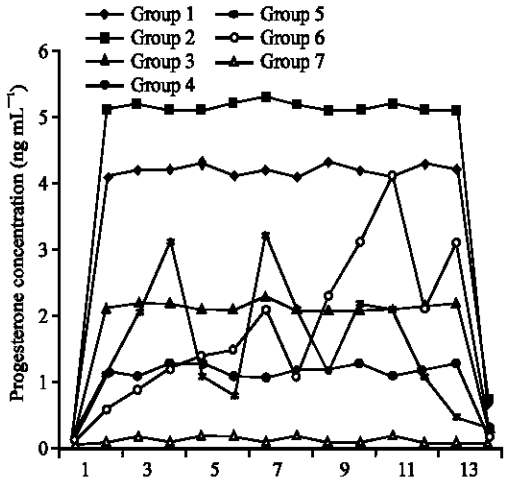

Fig. 1: Day elatve to progesterone administration

Removal of vaginal devices and implant and stoppage of i.m., injection resulted in rapid decline in the concentration of plasma progesterone to <1 ng mL^{-1} on day 13 relative to progesterone administration.

DISCUSSION

Administration of progesterone as intravagial device in camels significantly produced increased concentration of progesterone in peripheral circulation depending on the dose of the pessary. The concentration of the hormone was consistently uniform suggesting that progesterone was effectively absorbed from vagina of camel. Comparable studies have been performed in cows (Narasimha and Suryaprakasam, 1992) and ewes (Scudamore *et al.*, 1992) using intravaginal devices of progesterone. While, the possibility that the type of device or dosage of steroid might produce response such as follicular growth or ovum development has been investigated in several studies (Thompson *et al.*, 1990; Scudamore *et al.*, 1992), results have differed. Non of these studies involved monitoring of progesterone concentration during the period of steroid administration to establish whether, the difference in circulating steroid concentrations were related to the response.

The progesterone was administrated in silastic or sponge intravaginal devices and this route would allow for more uniform and possibly more physiological release rate compared to the non-uniform release provided by several injections (Bolta *et al.*, 1990). Indeed both SC

implant and intramuscular injection produced non-uniform release of progesterone in the peripheral circulation of camel possibly because of the initial damage to the injection site in the muscle, which was reflected in elevated plasma creatine kinase activity (Nouws *et al*., 1990). Changes in enzyme activities in blood such as LDH, ALP and AST can be a consequence of cell structural damage (Bogin *et al*., 1977; Sako *et al*., 2007) or specifically in uterine affections (Nigel *et al*., 1992). None of these enzymes have increased during intravaginal administration. Since, the experiment was performed during hot season, it is expected that animals may have undergone some degree of dehydration. Poor drug absorption from SC and i.m., injection site in dehydrated camel is expected due to reduced peripheral blood circulation (Al-Dughaym *et al*., 1998).

Removal of devices or implant or stoppage of injections of progesterone resulted in a rapid decline of the hormone in a way expected to follow a biexponential curve with a half-life of 26 min (Al-Busadah and Homeida, 2004).

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