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UTERINE ACTIVITY AFTER THE CONTINUOUS INFUSION OF NIFEDIPINE IN THE OVARECTOMISED CAMEL (*CAMELUS DROMEDARIUS*)

(With 2 Figures)

By

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تقلصات الرحم بعد الحقن المستمر لمحلول النيفيديبين فى النوق المستأصل مبايضها

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أجريت هذه الدراسة على ٣ نوق غير حوامل تم استئصال مبايضها ، سجلت التغيرات فى ضغط الرحم والتجويف البطنى باستخدام انابيب ذات الرأس البلونى. تم تحفيز تقلصات الرحم بالحقن اليومى لجرعة ٥ مغم من هرمون استراديول بنزويت طوال مدة التجربة. تراوح تردد تقلصات الرحم بين ٦-٩ لكل ١٠ دقائق بينما تراوح مداها بين ٢-٣ كيلو باسكال. نجح الحقن المستمر لمحلول النيفيديبين بجرعة ٠١٢ ر٠ مليمول لكل كيلو وزن حى فى الدقيقة الى خفض مدى تقلصات الرحم من ٣٣ر٢ ± ٢٩ر٠ كيلوباسكال الى ٦٧ر٠ ± ٢٩ر٠ (المتوسط الحسابى ± الانحراف المعيارى) بينما لم يتأثر تردد التقلصات بهذا الحقن.

SUMMARY

Three parous, non-pregnant camels were used in this study. Bilateral ovariectomy was performed in the three camels, and intrauterine and intraabdominal pressure changes were recorded using balloon-tipped catheters. Uterine contractions were induced and maintained in the ovariectomised camels by daily intramuscular injection of 5 mg estradiol benzoate throughout the experimental period. The frequency of uterine contractions varied from 6 to 9 per ten minutes, whereas the amplitude varied from 2 to 3 KPa. The continuous infusion of nifedipine at the dose rate of 0.012 mmol/kg/min for one hour succeeded in reducing the amplitude of uterine contractions in the three camels from a mean (±SD) of 2.33 ± 0.29 to 0.67 ± 0.29 KPa. However, the frequency of uterine contractions was not affected.

Keywords: *Uterine activity, Nifedipine, Camel.*

INTRODUCTION

Calcium antagonists or calcium channel blockers, such as nifedipine, are thought to inhibit the activation of smooth muscle by decreasing the amount of calcium entering the cell from the extracellular space (*FLECKENSTEIN, 1977*). In recent years, calcium antagonists have been used to suppress preterm labour in humans. They were found to be significantly more effective than β-mimitics

and are almost devoid of side-effects *(READ and WELLBY, 1986)*. The administration of nifedipine peripartum has been found to suppress uterine activity in different animal species, such as the ewe (*GOLICHOWSKI et al., 1985*), dog *(WURTH et al., 1986)* and rat *(TRACY and BLACKY, 1992)*.

The objectives of this study were to record uterine activity in ovariectomised camels, given daily injections of 5 mg estadiol benzoate, during continuous infusion of nifedipine.

MATERIALS and METHODS

Animals:

Three parous, non-pregnant female camels *(Camelus dromedarius)* aged 7-10 years and weighing 600-700 Kg were used in this study. Each animal was fed daily with a 2 Kg mixture of barley wheat bran and hay; water was provided ad libitum.

Implantation of balloon-tipped catheters:

Intrauterine and intraabdominal pressure changes were recorded using balloontipped catheters implanted in each uterine horn while a third one was left in the abdomen and sutured to the peritoneum and the adjacent muscles. Details of preparation and implantation have been described elsewhere *(AL-EKNAH and NOAKES, 1988 and AL-EKNAH et al., 1993)*.

Ovariectomy:

Bilateral ovariectomy was performed by laparotomy. After the exteriorisation of the ovary through the incision, the ovarian vessels were identified, separated from the mesovarian ligament and both structures firmly ligated with number 0 Mersilk. After both ovaries were excised, the genital tract was returned to the abdominal cavity. The preoperative and postoperative procedures were performed as previously described for the implantation of balloon-tipped catheters *(Al-EKNAH et al., 1993)*.

Recording of uterine activity:

Intrauterine and intraabdominal pressure changes were recroded continuously from at least two hours before and after nifedipine infusion. Pressure changes were recorded using pressure transducers (PT00, Bioscience, U.K.) Recording was performed with the animal in sternal recumbancy and the transducers were kept approximately at the same level as the balloons inside the animal. The equipment was calibrated so that there was a full scale deflection of 13.34 Kilo Pascals (KPa). The physiograph was run at 15 mm/min speed.

The frequency of contraction was quantified per 10 minutes and the amplitude was calculated in Kilo Pascals (1 KPa = 7.5 mm Hg). Simultaneous recording of intrauterine and intraabdominal pressure changes allowed elimination of the effects of such extraneous factors as rumination, defecation, grunting and crying. Uterine contractions were recorded from the left uterine horn, since uterine contractions were always greater in the left horn than in the right horn, but followed the same

pattern in the camel *AL-EKNAH et al. (1993).*

Hormonal treatment:

25 days after ovariectomy uterine activity ceased in all animals. Therefore, the animals were treated by daily intramuscular injections of 5 mg estradiol benzoate (Intervet, Holland) for 5 days before the infusion of nifedipine and throughout the experimental period. The effect of estradiol benzoate on uterine activity in ovariectomised camels has been previously studied *(HOMEIDA et al., 1993).*

Preparation and infusion of nifedipine:

Nifedipine solutions were made according to the instructions described by the Pharmaceutical Division of Bayer UK Ltd. Fresh, placebo, solvent for nifedipine was prepared from the following: 969 g polyethylene-glycol 400,60 g glycerine and 100 g distilled water. Shortly before infusion nifedipine was dissolved initially in the palcebo, solvent at a concentration not exceeding 6 g per ml solvent. The solution was homogenised for 15 minutes using a rotamixer and diluted to the concentration required using 0.9% sterile saline. The weighing, handling and infusion procedures of nifedipine were carried out using bottles and tubing protected from light, since nifedipine is highly light-sensitive especially when in solution (Bayer UK Ltd.). Nifedipine solution was continuously infused at a dose rate of 0.012 mmol/kg/min for one hour.

RESULTS

Daily injections of estradiol benzoate provoked uterine contractions in all the three camels with amplitude and frequency ranging between 2-3 KPa and 6-9 contractions per 10 min, respectively (Fig. 1a).

The continuous infusion of nifedipine solution at a dose rate of 0.012 mmol/kg/min for one hour resulted in a reduction of the amplitude of uterine contractions in the three camels from 2.33 ± 0.29 KPa before the start of infusion to a minimum of 0.67 ± 0.29 KPa one hour latter (Figs. 1a, b, c and). However, the frequency of uterine contractions was not affected in the three animals during the whole period of the infusion. The amplitude of uterine contractions regained its normal pattern 90 minutes after the cessation of the infusion.

DISCUSSION

In a previous study, during the oestrus cycle of the camel (*AL-EKNAH et al., 1993),* it was concluded that uterine activity is dependent upon oestrogen level. Therefore, bilateral ovariectomy succeeded in reducing uterine activity until complete cessation *(HOMEIDA et al., 1993).* Daily intramuscular injection of estradiol benzoate re-established uterine activity. The mechanism responsible for the stimulatory effect of oestrogen on myometrial activity has been shown to be due to the formation of gap junctions *(GARFIELD et al., 1980),* which provide low resistance couping for communication between cells.

From the results obtained in this study it appears that uterine activity in the ovariectomised camels is suppressed following nifedipine infusion. However, the uterus steadily regained its contractility when infusion was stopped.

The infusion rate of nifedipine chosen in this study (0.012 mmol/Kg/min) was more than the maximum rate given to human viz. 5 mg/h (data from Syntex Pharmaceuticals Ltd., UK). The increase in rate of infusion produces a positive effect of nifedipine on uterine activity *(TRACY and BLACK,1992).*

Extracellular calcium, which enters through specialised calcium channels of the cell membrane, is more important for the smooth muscle activity than the intracellular calcium because the diffusional distance between the extracellular space and the contractille elements is short, and the rate of contraction is slow enough to be supported by the transmembrane calcium influx *(HUSZAR, 1984).* Therefore, nifedipne blocks the entry of calcium into the intracellular space, and hence causing cessation of uterine activity. Whether nefidipne can be used to delay premature labour in camels or not is still to be elucidated.

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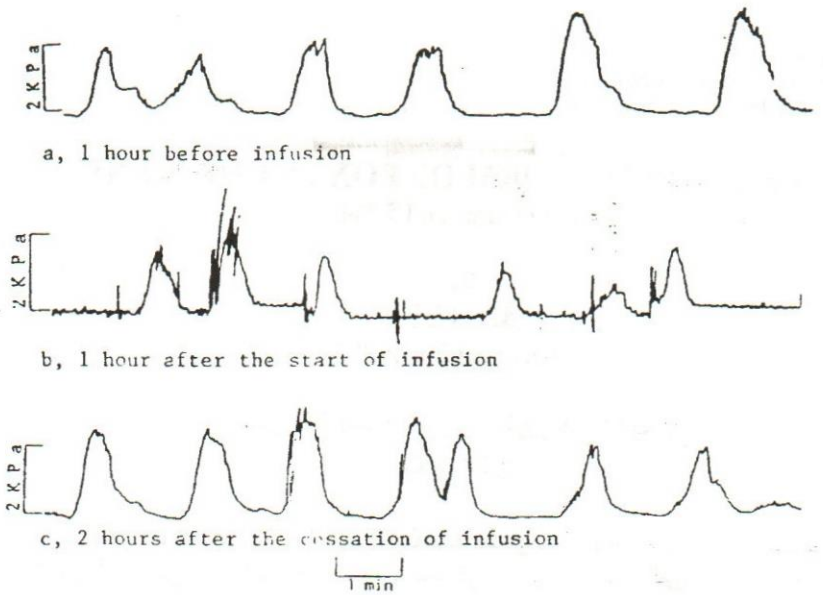

Fig. 1. Pattern of uterine contractions before, during and after the continuous infusion of nifedipine in camel 1.

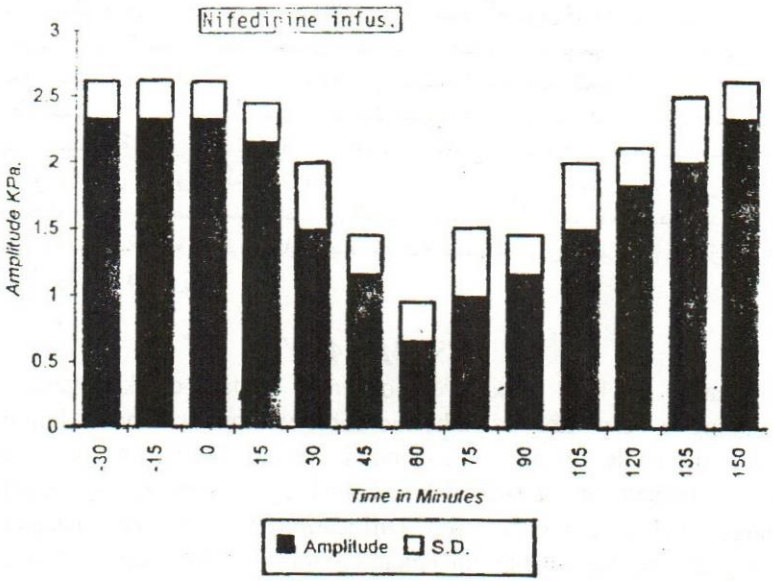

Fig 2. Mean and S.D. amplitude of uterine contractions in the three ovariectomized camels continuously infused with nifedipine solution .