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Changes in peripheral hormone levels after mid-gestation termination of pregnancy with aglepristone in rats

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ABSTRACT

The aim of this study was to evaluate the changes in concentrations of plasma hormones after mid-gestation termination of pregnancy with aglepristone in albino rats. Methods: Fifteen (15) pregnant albino rats (*Rattus norvegicus*) were randomly allocated to two groups. Aglepristone (Alizin®) was administered to group I (n = 7) subcutaneously at a dose of 10 mg/kg b.w. on days 10 and 11 of gestation (24 h apart) whereas group II (n = 8) were injected with an equivalent volume (0.33 mL/kg) of sterile water for injection (Dana®) via the same route and on the same days as indicated for group I. Blood samples for hormonal assay were collected from both groups and the mean serum concentrations of progesterone, oestradiol, LH and FSH on gestation days 8 (prior to treatment), 12, 16, and 20 were determined using the enzyme immunoassay (EIA) technique. Results: Bloody vulval discharges (abortion) were observed in all the aglepristone-treated rats within 24.7 ± 3.8 h after the first injection of aglepristone and lasted for 47 ± 5.7 h post-treatment. By day 16 post-mating (6 days after first treatment), the aglepristone-treated rats had significantly ($P<0.05$) lower serum concentrations of oestradiol (17.07 ± 3.54 pg/mL) and progesterone (11.64 ± 4.3 ng/mL) than group II (34.19 ± 6.98 pg/mL; 88.44 ± 18.52 ng/mL respectively). By day 20 post-mating, the mean serum FSH level of group I was significantly higher (13.61 ± 10.21 mIU/mL) than that of group II (3.84 ± 0.87 mIU/mL; $P<0.05$). Conclusion: Aglepristone was very effective in termination of pregnancy when administered mid-gestation to albino rats. However, the hormonal changes observed following the termination of pregnancy with aglepristone in rats differed from the reports in dogs and cats.

Key words: aglepristone, antiprogestin, abortion, gestation, rat, hormones

Introduction

Specific approaches in endocrine research have involved the development of competitive hormone receptor blockers (HOFFMANN and SCHULER, 2000) which is part

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of the global effort to develop new drugs to widen therapeutic alternatives for diseases and to permit better control of the oestrous cycle and fertility in general (GOBELLO, 2006). Antiprogestins or progesterone-antagonists are synthetic steroids that bind with great affinity to progesterone receptors, competitively displacing endogenous progesterone and thus preventing progesterone from exerting its biological effects (HOFFMANN et al., 2000). Aglepristone, an analogue of mifepristone, was formulated as an injectable and became the first antiprogestin licensed only for veterinary use (ÖZALP et al., 2008). The hydrophobic side chain at C17 is responsible for the high-affinity receptor binding of aglepristone, while the additional aromatic ring at C11 with a dimethyl-amino group is responsible for the changes in receptor conformation leading to a suppression of transcription (HOFFMANN and SCHULER, 2000).

Due to the importance of progesterone in the maintenance of pregnancy, aglepristone has been applied most prominently in the prevention or termination of pregnancy in bitches (GALAC et al., 2000; SCHÄFER-SOMI et al., 2007) and in queens (GEORGIEV and WEHREND, 2006; GOERICKE-PESCH et al., 2010). Although aglepristone is marketed for pregnancy termination in canines, it has been used in rabbits to prevent implantation (ÖZALP et al., 2010) and to induce abortion (ÖZALP et al., 2008). In other reports, aglepristone was also used to induce parturition in dogs (FIENI et al., 2001; BAAN et al., 2005). Furthermore, aglepristone has been applied clinically in the treatment of several progesterone-related disease conditions in animals such as pyometra in cats (HECKER et al., 2000; NAK et al., 2009) and dogs (TRASCH et al., 2003; GÜRBULAK et al., 2005); hypersomatotropism in dogs (BHATTI et al., 2006); vaginal fibroma in dogs (ROLLÓN et al., 2008); mucometra in cats (GEORGIEV and WEHREND, 2005); mammary fibroadenomatosis in cats (GÖRLINGER et al., 2002; VITÁSEK and DENDISOVÁ, 2006), and metritis-pyometra complex in guinea pig (BARON VON ENGELHARDT, 2006).

Clinical applications of antiprogestins in humans and animals appear to be generally limited because of potential reproductive hazards (SPITZ, 2003; SITRUK-WARE and SPITZ, 2003), a poor understanding of the precise mechanisms of the divergent antiprogestin effects on the endometrium (CHWALISZ et al., 1998; CHWALISZ et al., 2005) and a potential risk of altered estrogen action as the result of prolonged use (CHWALISZ et al., 1998; GOPALKRISHNAN et al., 2003). Thus our objective in this study was to evaluate the changes in concentrations of plasma hormones after mid-gestation termination of pregnancy with aglepristone in albino rats.

Materials and methods

Animals. Experiments were conducted in accordance with the regulations and ethics governing animal welfare and research of the University of Nigeria. Healthy albino rats (*Rattus norvegicus*) of the Sprague-Dawley strain, comprising 15 females (12-14 weeks

old) and 7 males (15 weeks old) were used for the study. The animals were housed in metallic cages at room temperature (28-32 °C) in the Laboratory Animal House of the Department of Veterinary Obstetrics and Reproductive Diseases, University of Nigeria Nsukka. Commercial feed (Vital® Growers feed, GCOML, Jos, Nigeria) and water were provided *ad libitum* for the duration of the study.

Determination of mating. The vaginal plug method as described by OCHIOGU et al. (2006) was used to determine successful mating in the female rats. Following the introduction of groups of two female rats to a male of proven fertility, vaginal wet smears were grossly examined every 12 hours for the presence of protein coagulates (remnants of the copulatory plug) as evidence of successful mating. The day of observation of vaginal coagulates was designated day 1 of pregnancy (ORIHUELA et al., 2009). The body weights of the female rats were determined on day 1 of pregnancy, and subsequently at four day intervals.

Induction of abortion with aglepristone. Simple randomization procedure was used to allocate fifteen pregnant rats to either the test group (I) or the control group (II). Aglepristone (Alizin®, Virbac, Suffolk, United Kingdom) was administered to group I (n = 7) subcutaneously, below the loose skin over the neck, at a dose of 10 mg/kg b.w. on days 10 and 11 of gestation (24 h apart). Rats in group II (n = 8) were injected with an equivalent volume (0.33 mL/kg) of sterile water for injection (Dana®, Nigeria) via the same route and on the same days as indicated for the test group. The site of subcutaneous injection was gently massaged for a few seconds. The time of treatment was recorded and all the animals were placed on close observation. Abortion was determined in group I by physical observation of bloody vaginal discharges following aglepristone treatment.

Hormonal assay. Blood samples for hormonal assay were collected from both groups via the retro-orbital venous plexus on days 8 (prior to first treatment), 12, 16 and 20 post-mating. A microhaematocrit capillary tube was inserted into the medial canthus of the eye until the bony orbit was contacted, then withdrawn slightly to allow the blood to flow through the capillary tube into a collection test tube. Collected blood was allowed to stand for 30-45 min in order to coagulate and then centrifuged at 3000 × g for 15 min. Following this, serum was aspirated from the supernatant, placed in microcentrifuge tubes and stored at -20 °C until analysis. The mean serum concentrations of progesterone (P_4), oestradiol (E_2), luteinising hormone (LH) and follicle-stimulating hormone (FSH) on gestation days 8, 12, 16, and 20 were determined for both groups using the enzyme immunoassay (EIA) test kit (BioCheck®, USA). The absorbance was read spectrophotometrically within 15 min with a microtitre plate reader (Teco™, USA) set at an absorption wavelength of 450 nm. The lower limit of detection for progesterone was 0.0625 ng/mL, oestradiol (10 pg/mL), FSH (2.5 mIU/mL) and LH (1.0 mIU/mL).

Data Analysis. Statistical analysis was performed using SPSS software® (Version 15.0 for Windows, SPSS Inc., Chicago, IL, USA). Mean and standard deviations (SD) were calculated for data groups. The serum hormone concentrations of the control and the aglepristone-treated groups were compared on days 8, 12, 16, and 20 of gestation using the Student's *t*-test (two-tailed). Within-group hormone concentrations on the different days of gestation were analysed by One-way Analysis of Variance (ANOVA) and the variant means separated by the Least Significance Difference (LSD) test. Values are expressed as mean ± SD. Results were considered significant when $P<0.05$.

Results

Abortion. Bloody vulval discharges (abortion) were observed in all the aglepristone-treated rats (group I) within 24.7 ± 3.8 h after the first injection of aglepristone. Vaginal discharges lasted for 47 ± 5.7 h, during which time aborting rats often retreated to corners of the cages and had lowered feed intake. The rats in group II did not show any abnormalities in behaviour nor record any vulval discharges following treatment with the placebo. Rats in group II (n = 8) had normal pregnancy with an average gestation length of 21.3 ± 0.7 days, and delivered a mean litter size of 7.7 ± 2.0 with a litter weight of 44.0 ± 6.8 g.

Body weights and hormonal profile after abortion. A steady increase in body weight was observed for rats in group II up to day 20 of gestation. However, 6 days after the first treatment (by day 16 post-mating), the aglepristone-injected rats recorded a significantly lower ($P<0.05$) group weight (175.9 ± 7.7 g) than the rats in group II (197.6 ± 9.3 g). By day 20 post-mating, group II rats weighed 231.4 ± 13.1 g while group I weighed significantly less (177.6 ± 7.3 g; $P<0.05$) (Fig. 1).

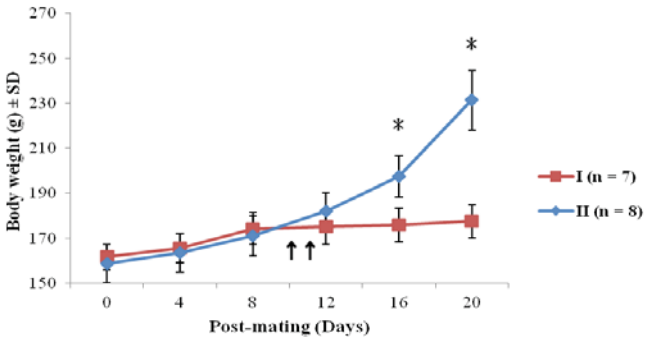

Fig. 1. Mean (± SD) body weights of aglepristone-treated albino rats (group I) and the control (group II). (↑ = days of injections). * = statistically significant differences at $P<0.05$

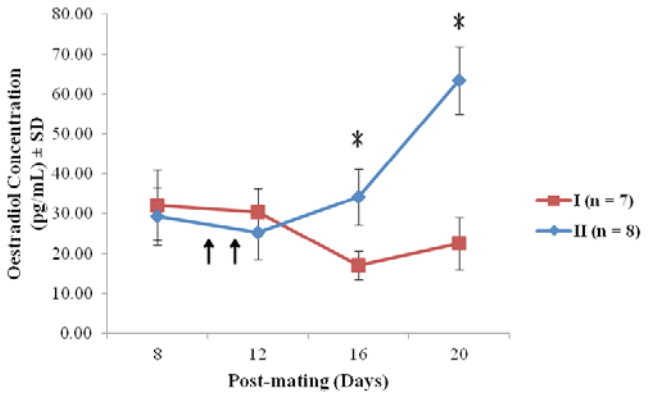

Fig. 2. Mean (± SD) serum oestradiol (E_2) concentrations of aglepristone-treated albino rats (group I) and the control (group II). (↑ = days of injections); * = statistically significant differences at P<0.05

There was no significant difference in the serum concentrations of E_2 before treatment and by day 12 post-mating in group I (30.43 ± 5.91 pg/mL) and group II (25.25 ± 6.76 pg/mL; P>0.05). However, 6 days after first treatment (by day 16 post-mating), the serum E_2 levels of the aglepristone-treated rats had decreased significantly to 17.07 ± 3.54 pg/mL when compared with group II (34.19 ± 6.98 pg/mL; P<0.05). By day 20 post-mating, the serum E_2 level of group I was still significantly lower (22.64 ± 6.54 pg/mL) than that of group II (63.5 ± 8.52 pg/mL; P<0.05) (Fig. 2). Serum P_4 concentration was not significantly different before treatment and by day 12 post-mating in group I (49.57 ± 9.45 ng/mL) and group II (46.25 ± 7.74 ng/mL; P>0.05). By day 16 post-mating, the peripheral P_4 level of the aglepristone-treated rats was significantly lower (11.64 ± 4.3 ng/mL) than that of group II (88.44 ± 18.52 ng/mL; P<0.05). By day 20 post-mating, the P_4 level of group II had decreased sharply to 27.75 ± 11.30 ng/mL but was still significantly greater than that of group I (14.71 ± 4.86 ng/mL, P<0.05) (Fig. 3).

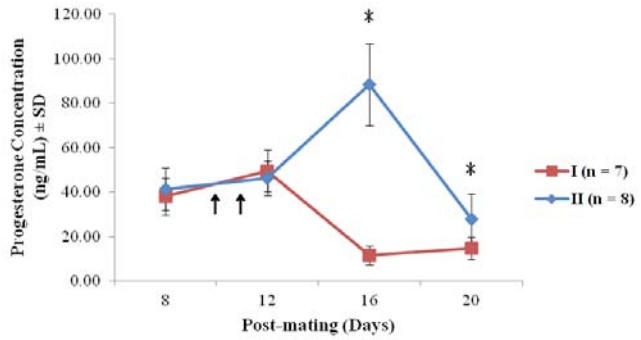

Fig. 3. Mean (± SD) serum progesterone (P_4) concentrations of aglepristone-treated albino rats (group I) and the control (group II). (↑ = days of injections); * = statistically significant differences at $P<0.05$

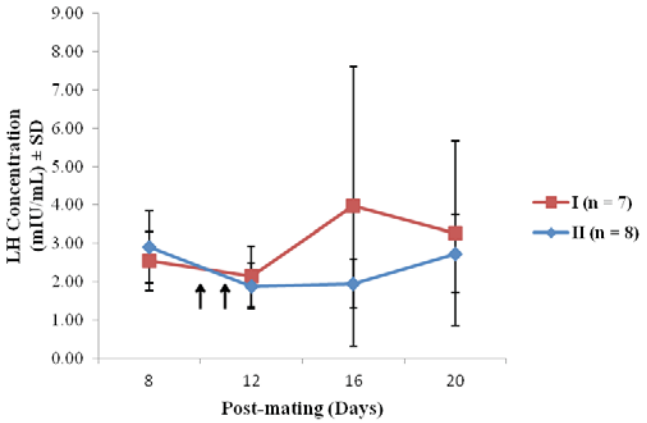

Fig. 4. Mean (± SD) serum luteinising hormone (LH) concentrations of aglepristone-treated albino rats (group I) and the control (group II). (↑ = days of injections)

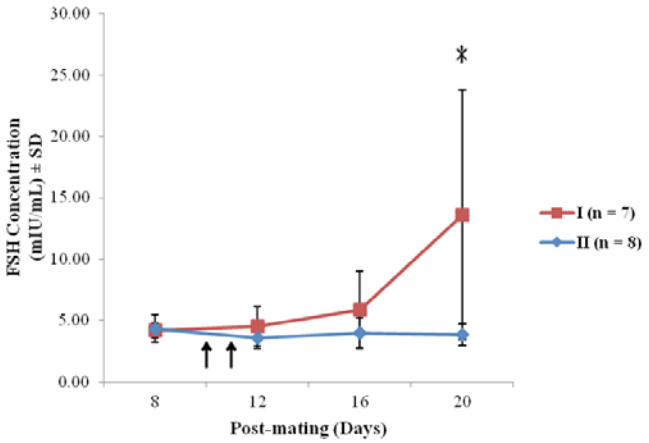

Fig. 5. Mean (± SD) serum follicle-stimulating hormone (FSH) concentrations of aglepristone-treated albino rats (group I) and the control (group II). (↑ = days of injections). * = statistically significant differences at P<0.05

There was no significant difference in the serum concentrations of LH before treatment and by day 12 post-mating in group I (2.14 ± 0.79 mIU/mL) and group II (1.89 ± 0.59 mIU/mL; P>0.05). However, 6 days after first injection of aglepristone (by day 16 post-mating), the serum LH level of group I was higher (3.97 ± 3.65 mIU/mL) than that of group II (1.95 ± 0.64 mIU/mL) although this was not found to be statistically significant (P>0.05) (Fig. 4). The serum FSH concentrations showed no significant differences up to day 16 post-mating in group I (5.83 ± 3.17 mIU/mL) and group II (3.98 ± 1.20 mIU/mL; P>0.05). However, by day 20 post-mating, the serum FSH level of group I was found to be significantly higher (13.61 ± 10.21 mIU/mL) than that of group II (3.84 ± 0.87 mIU/mL; P<0.05) (Fig. 5).

Discussion

Aglepristone injected subcutaneously was generally well tolerated in the treated rats. Aglepristone caused abortion in 100% of treated rats, which is consistent with reports of the high efficacy of the antiprogestin in dogs (GALAC et al., 2000; SCHÄFER-SOMI et al., 2007) and rabbits (ÖZALP et al., 2008). Other studies in cats reported lower efficacy rates of 88.5% (FIENI et al., 2006) and 87% (GEORGIEV and WEHREND, 2006).

As observed in this study, mean plasma P_4 concentration in the control pregnant rats peaked around day 16 of gestation, and began to decline rapidly around day 20 of

gestation, whereas E_2 level increased gradually up to day 16 of gestation, but peaked rapidly around day 20 of gestation. These observations are in agreement with reports of patterns of P_4 and E_2 plasma concentrations in normal pregnant rats (PURI and GARFIELD, 1982; MAGNESS, 1998; AL-BADER, 1999).

There was no significant difference in P_4 concentration during abortion between the control and aglepristone-treated rats. This observation is in agreement with reports that aglepristone acts as a true progesterone antagonist on the uterus, without any effect on luteal function in cats (FIENI et al., 2006; GEORGIEV and WEHREND, 2006), bitches (FIENI et al., 2001; GALAC et al., 2000) and rabbits (ÖZALP et al., 2008). Post-abortion, however, there was significant decrease in the serum P_4 levels of the aglepristone-treated rats. This observation is in agreement with the report in rabbits (ÖZALP et al., 2008) but differs from reports in bitches (GALAC et al., 2000; SCHÄFER-SOMI et al., 2007) in which serum P_4 levels remained high for up to 45 days after the beginning of abortion. Although ÖZALP et al. (2008) did not give any explanation for this decrease in P_4 level in rabbits, we inferred that placental degeneration and the loss of placental luteotrophic lactogens led to the lyses of corpus luteum of pregnancy and the consequent fall in P_4 levels in rats. Similarly, the loss of placentally-derived androgens required for ovarian E_2 synthesis might explain the significant decrease in serum E_2 levels following abortion in the test group.

Detailed studies on the effects of progesterone receptor antagonists on the hypothalamic-pituitary-ovarian axis are lacking. Post-abortion, however, an increase in serum concentrations of LH and FSH was observed in the aglepristone-treated rats. This increase appears to be a consequence of the significant decrease in serum E_2 and P_4 levels post-abortion, and the subsequent lack of negative feedback control on the release of FSH and LH in the aglepristone-treated rats. The differences in the onset and duration of abortion in the individual aglepristone-treated rats and the pulsatile release of LH post-abortion might explain the variations in the serum concentrations of LH at the times of assay.

The decrease in feed intake during abortion, and subsequently the vaginal bleeding, foetal loss and decrease in P_4 concentration, all contributed to the significant decrease in weight gain in the aglepristone-treated rats as observed in this study.

In conclusion, aglepristone was very effective in termination of pregnancy when administered mid-gestation to albino rats. The hormonal changes observed following the termination of pregnancy with aglepristone in rats differed from the reports in dogs and cats. However, it is recommended that further investigations be carried out on the endocrine effects following prolonged use or repeated induction of abortions with aglepristone.

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SAŽETAK

Cilj istraživanja bio je procijeniti promjene u koncentraciji hormona plazme albino štakora nakon što je u sredini gravidnosti izazvan pobačaj aglepristonom. Petnaest gravidnih albino štakorica (*Rattus norvegicus*) razdvojeno je slučajnim izborom u dvije skupine. Aglepriston (Alizin®) je bio primijenjen u skupini I (n = 7) potkožno u dozi od 10 mg/kg tjelesne mase 10. i 11. dana gravidnosti (u razmaku od 24 sata) dok je skupini II (n = 8) u iste dane i na isti način bio primijenjen volumni ekvivalent (0,33 mL/kg) sterilne vode za injekcije (Dana®). Uzorci krvi za određivanje hormona bili su prikupljeni od obiju skupina te je, uz pomoć imunoenzimne analize (EIA), 8. dana gravidnosti (prije tretmana), a zatim 12., 16. i 20. dana u serumu utvrđena srednja koncentracija progesterona, estradiola LH i FSH. Krvavi iscjedak iz vulve (pobačaj) ustanovljen je u svih štakorica kojima je dan aglepriston unutar 24,7 ± 3,8 sati od prve injekcije. Iscjedak je trajao 47 ± 5,7 sati nakon davanja. Šesnaestog dana nakon parenja (6 dana nakon prvog davanja), štakorice koje su dobile aglepriston imale su statistički značajno ($P<0,05$) nižu serumsku koncentraciju estradiola (17,07 ± 3,54 pg/mL) i progesterona (11,64 ± 4,3 ng/mL) u odnosu na štakorice druge skupine (34,19 ± 6,98 pg/mL; 88,44 ± 18,52 ng/mL). Do 20. dana nakon parenja, srednja serumska razina FSH u skupini I bila je statistički značajno viša (13,61 ± 10,21 mIU/mL) u odnosu na skupinu II (3,84 ± 0,87 mIU/mL; $P<0,05$). Zaključuje se da je aglepriston, primijenjen u srednjoj trećini gravidnosti, bio vrlo učinkovit za prekidanje gravidnosti albino štakorica. Ipak, hormonske promjene utvrđene nakon prekida gravidnosti štakorica aglepristonom, bile su različite od izvješća za pse i mačke.

Ključne riječi: aglepriston, antiprogestin, pobačaj, gravidnost, štakor, hormoni