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RESEARCH ARTICLE

Effects of an antiprogesterone agent, on serum estrogen and progesterone levels in rats

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Abstract

Objective: To investigate the effect of mifepristone on the levels of hormones of rats.
Study Design: Laboratory based randomized controlled trial
Method: Sixty adult female rats were divided randomly into two groups, comprising of 30 animals in each group. In-group A 1ml of normal saline was given orally daily for three months while in group B mifepristone was given orally in a dose of 1mg/kg body weight daily for three months. All the animals were sacrificed next day after the last oral dose
Results: The mean serum estrogen level was (83.6±1.2 pg/ml), which was higher than that of the control group. The difference was found significant statistically when compared with the control group. The mean progesterone level was 2.8 ± 0.09 ng/ml which was lower than that of the control group.The difference was found significant statistically when compared with the control group.Progesterone antagonist application lowered the plasma concentration of progesterone.
Conclusion: In conclusion, mifepristone lowered the plasma concentration of progesterone while estrogen concentration was raised in the rat.

Introduction

Progesterone is required for the development of the endometrium in preparation for pregnancy During pregnancy, progesterone promotes a quiescent uterine myometrium and a closed cervical os[1Connelly OM. 2001].
Progesterone is essential to these functions, in theory, blockade of its action would result in infertility or abortion. Steroid antagonists of progesterone have been developed that block progesterone action at the receptor level .Progesterone antagonists were hailed as providing new venues for exploration of progesterone action and for treatment of progesterone-dependent conditions. Much of this speculation was based on the assumption that progesterone antagonists would simply reverse or inhibit progesterone actions[2]. Benakanakere C 2009, Besch-Williford M 2009, Ellersieck R 2009, Hyder SM 2009

Material & Methods

These laboratory based randomized controlled trials were conducted at the department of Anatomy, Army Medical College Rawalpindi from Jan 2007 to March 2007. Institutional Ethical Committee of Army Medical College Rawalpindi approved all the procedures. Sixty healthy adult female Sprague Dawley rats weighing 200-300g were procured from the National Institute of Health Sciences Islamabad. The animals were randomly divided into two groups having 30 rats in each.
Group A (Control)
Thirty female rats were given 1ml of normal saline orally daily for three months.
Group B (Experimental)
Thirty female rats were given the drug (Mifepristone) orally in a dose of 1mg/kg body weight daily for three months.

The animals of both groups were weighed at the start and at the end of the experiment. Animals were anesthetized by an overdose of ether, cotton was soaked in ether and placed into the jar. The animals were placed on a clean sheet of paper on a dissecting board and while still keeping continuously anesthetized by a bottle covering the head of the rat containing swabs soaked in ether, the chest was palpated for locating the heart. Once located, it was penetrated by the needle of 5 ml plastic aseptic syringe to draw 2 ml blood directly from the heart and then the animal was killed. Collected blood samples were then immediately transferred into labeled plastic pipettes, which were kept in a rack, refrigerated at- 21'C for a few days till they were centrifuged later on to separate serum, which was kept in labelled bottles for measurement of estrogen and progesterone levels.

STATISTICAL ANALYSIS

The data were analyzed statically using SPSS version 13. Independent samples't-test was used to check the statistical significance of difference between control and experimental groups for different variables .The *P* value of <0.05 was considered as significant

OBSERVATIONS AND RESULTS

This study was designed to evaluate the levels of estrogen and progesterone hormones in rat following treatment with mifepristone a potent antiprogesterone drug. The mean serum estrogen and serum progesterone level in the control group were 41.7±0.66pg/ml and 5.5±0.8ng/ml respectively (Appendix I) The animals of the experimental group were fed and kept under the same conditions as that of the control group. The animals remained healthy and active at the start of the experiment, but became sluggish by the end. The mean serum estrogen level was (83.6±1.2 pg/ml), which was higher than that of the control group. The difference was found significant statistically when compared with the control group. The mean progesterone level was 2.8 ± 0.09 ng/ml which was lower than that of the control group (Appendix II) .The difference was found significant statistically when compared with control group (*p* =0. 001) *(Table. 1).*

DISCUSSION

The dose of the drug having antiprogesterone properties in rodents was administered orally, representing the human dosing route and a desirable approach to drug delivery. Antiprogesterone, depending upon the physiological status of the animal has a paradoxical agonist and antagonist activities in uterine compartments of rats and humans[3Sukjum LS.,2005]. The animals remained healthy and active at the start of the experiment, but became sluggish by the end. This may be due to long term treatment with the antiprogesterone (mifepristrone).

Progesterone receptors (PR) mediate multiple aspects of female reproduction and are important targets for reagents that can modulate progesterone-dependent events. Many such reagents have been developed, and they range from full PR antagonists (PAs) to compounds with mixed agonist/antagonist actions, currently known as selective progesterone receptor modulators (SPRMs) Abundant evidence in the literature shows that steroid hormones play an active role in regulating cyclic endometrial vascularchanges and vascular permeability that are essential for endometrial physiologyand for successful nidation and reproduction[4De Vivo I 2004, Hankinson SE 2004, Colditz GA 2--4, Hunter DJ 2004.]

As the expression of estrogen receptors in our case was associated with high plasma oestradiol concentrations, it is possible that the expression of these receptors can be oestradiol independent. The chronic antiprogestines administration also inhibits estrogen-dependent endometrial cell proliferation and growth. This endometrial antiproliferative effect is the basis of the clinical use of antiprogestines to control various diseases such as endometriosis[5Jeffrey R1998, Goldberg, MD1998, Marcus G1998, Plescia MD1998, MPH, Geraldine D Anastasio 1998]. Except for a minimal decrease in serum estradiol levels, antiprogestines had little effect on folliculogenesis, timing of ovulation, or duration of the menstrual cycle when given during the first three days of the cycle[6O.D. Slayden2006, M.B. Zelinski2006, K. Chwalisz, H2006. Hess-Stumpp, R.M 2006.] When given during the midfollicular phase at single doses of 10 or 100 mg, LH and follicle-stimulating hormone (FSH) levels decreased in proportion to the plasma estradiol levels at the time the dose was given[7 S. Schäfer-Somi 2007, O.A. Aksoy, H.B 2007. Beceriklisoy, at 2007. Einspanier, H.O 2007. Hoppen , S. Aslan 2007.] ·Thus, the ability of RU 486antiprogesterone to reduce gonadotropins seems dependent on prior exposure to estrogen.

Serum progesterone levels declined in experimental groups after mifepristone administration. The level of estrogen hormone was elevated in the experimental group as compared with the control group. Previous reports concerning the effect of mifepristone on progesterone secretion have not been entirely congruent[8Astrid Petersen, 2005]. In a study using 200 mg of mifepristone, no statistically significant changes in the progesterone levels were observed in the 2-day follow-up[9Van Look PFA 1994, Ven herizen H, 1994]. In another study, with 600 mg mifepristone, progesterone levels increased on day 1 and then decreased significantly[10Baird DT 1999, Glasier AF,1999]. Apart from its effects on the endometrium, progesterone exerts

important activity on the breast, cervix, lipids, pituitary-hypothalamic unit, and brain. An antiprogestin would block or alter these effects. The paradoxical effects (Mifepristone both raises and lowers progesterone levels) have also been explained by the hypothesis that mifepristone can act either by preventing the progesterone effect or in a way that is similar to that of progesterone, which always stimulates its own secretion by autoregulation. It is possible that these effects are different depending on the duration of pregnancy.

Appendix-I

Levels of Progesterone and Estrogen Hormones of Control Group

Animal no	PARAMETERS	
	Progesterone ng/ml	Estrogen pg/ml
1	2.36	40
2	2.5	39.5
3	3.6	42.5
4	3.8	43
5	2.8	46
6	2.5	43
7	2.6	40.5
8	2.8	38.5
9	3.5	48.5
10	3.0	43
11	2.0	35
12	2.5	38
13	2.8	39.5
14	2.5	38
15	3.6	43
16	2.6	39
17	2.5	42.5
18	2.3	37
19	2.8	39.8
20	2.8	46
21	2.36	43.5
22	3	40.5
23	3.5	48.5
24	3.5	48
25	2.0	38.3
26	2.3	39.5
27	2.3	48.5
28	3.8	40
29	2.36	43
30	3.6	40
AVERAGE	5.54	41.74
SD	0.536	3.463
SE	0.8669	0.66215

Appendix –II

Levels of Progesterone and Estrogen Hormones of Experimental Group

Animal no	PARAMETERS	
	Progesterone ng/ml	Estrogen pg/ml
1	5.6	40
2	5.6	39.5
3	5.22	42.5
4	5.9	43
5	6.1	46
6	4.83	43
7	5.52	40.5
8	5.6	38.5
9	5.3	48.5
10	4.9	43
11	5.1	35
12	5.3	38
13	6.5	39.5
14	5.3	38
15	6	43
16	5.2	39
17	5.1	42.5
18	5.5	37
19	5.1	39.8
20	6.2	46
21	6.1	43.5
22	5.5	40.5
23	6.5	48.5
24	4.9	48

25	5.25	38.3
26	5.65	39.5
27	6.3	48.5
28	5.2	40
29	5.8	43
30	5.1	40
Average	2.8193	83.66
SD	0.467	6.53
SE	0.0994	1.20989

TABLE-1
Statistical Significance of Progesterone and Estrogen Levels of Control and Experimental Groups

Parameters	Control (n=30) Mean ± SE	Experimental (n=30) Mean ± SE	*p* value
Progesterone ng/ml	5.5±0.8	2.8±0.09	p =0.001
Estrogen pg/ml	41.7±.66	83.6. ±1.2	p =0.001

KEY: n = number of animals
Significant $P< 0.05$

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