Original Article

Gynecologic and Obstetric Investigation

Gynecol Obstet Invest 2004;58:105–108
DOI: 10.1159/000078842

Received: May 6, 2003
Accepted after revision: April 13, 2004
Published online: June 7, 2004

Pharmacokinetics of Natural Progesterone Vaginal Suppository

Helena von Eye Corleta[a,b] Edison Capp[a,c] Maria Beatriz Cardoso Ferreira[d]

[a]Department of Obstetrics and Gynecology, Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul; [b]Núcleo Gerar – Reprodução Humana – Hospital Moinhos de Vento, Porto Alegre, Brazil; [c]Department of Physiology, Universidade Federal do Rio Grande do Sul, and [d]Department of Pharmacology, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil

Key Words

Progesterone · Pharmacokinetics · Vaginal suppositories · In vitro fertilization · Endometrial protection

Abstract

Natural and synthetic progesterone have been used to treat luteal insufficiency, premenstrual syndrome, and in infertile patients. The transvaginal route has advantages, such as lack of local pain, avoidance of first-pass hepatic metabolism, rapid absorption, high bioavailability and local endometrial effect. The aim of this study was to evaluate the pharmacokinetic of natural progesterone administered as vaginal suppositories of 25, 50 or 100 mg. Thirty-five healthy ovulating patients, 31.54 ± 1.29 (mean ± SEM) years old, in the follicular phase of the menstrual cycle (between days 7 and 10) participated in the study. They were separated in three groups and received vaginal suppositories containing either 25, 50 or 100 mg of natural progesterone. Progesterone serum concentration reached maximal levels within 2 or 3 h after the administration and was similar for the three groups (7.27 ± 2.8 ng/ml; 8.84 ± 3.14 ng/ml; 9.82 ± 9.8 ng/ml, respectively). This study demonstrated that vaginally administered progesterone could reach levels that are similar to those obtained in ovulatory and luteal phases. The progesterone regimen for adequate endometrial protection and in vitro fertilization (IVF) programs still remains to be studied.

Introduction

Progesterone has been used to treat luteal insufficiency, premenstrual syndrome, and in infertile patients. Synthetic active progesterones have been available since 1950. They form two main groups of synthetic progestins: the 17-hydroxyprogesterone derivates and the 19-nortestosterone derivates [1]. The use of these synthetic progestins is limited in human reproduction because of the side effects in implantation and possible teratogenic effects [2].

Natural progesterone can be administered by oral, intramuscular, or vaginal routes. The different ways of administering progesterone can determine very different concentrations of serum progesterone [3]. Absorption of progesterone from the intestinal tract is prompt, but natural progesterone is quickly inactivated by rapid metabolism in liver and intestine when taken orally. Because of

KARGER

Fax + 41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

0378–7346/04/0582–0105$21.00/0

Accessible online at:
www.karger.com/goi

Dra. Helena Corleta
Rua Ramiro Barcelos, 910 cj 905
90035–001 Porto Alegre, RS (Brazil)
Tel. +55 51 3311 56 99, Fax +55 51 3311 65 88, E-Mail hcorleta@portoweb.com.br

Table 1. Baseline characteristics of the study group

	Progesterone dose, mg			All (n = 35)
	25 (n = 13)	50 (n = 12)	100 (n = 10)	
Age*	29.61 ± 2.18	34.00 ± 2.06	31.10 ± 2.46	31.54 ± 1.29
Height, cm**	159.9 ± 0.19	159.8 ± 0.19	161.8 ± 0.26	160.4 ± 0.12
Weight, kg***	58.30 ± 1.85	60.23 ± 1.80	61.46 ± 4.49	59.86 ± 1.54
BMI, kg/m^{2},#	22.80 ± 0.62	23.66 ± 0.86	20.34 ± 2.50	23.25 ± 0.51

Data are expressed as mean ± SEM. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m).

* $p = 0.360$; ** $p = 0.787$; *** $p = 0.717$; # $p = 0.784$, by one-way ANOVA.

rapid inactivation of progesterone when it is administered orally, the intramuscular and vaginal routes are preferable. Several attempts to improve oral bioavailability of natural progesterone were investigated. Reduction of the particle size of progesterone (micronization) enhances bioavailability. However, the micronized form did not provide adequate concentrations throughout the day [4], and the absorption is still erratic [5].

The advantages of the transvaginal route are lack of side effects such as local pain, avoidance of first-pass hepatic metabolism, rapid absorption, high bioavailability and local endometrial effect (first-pass uterine effect) [1, 6, 7].

The aim of this study was to evaluate the pharmacokinetics of natural progesterone administered as vaginal suppositories of 25, 50 or 100 mg.

Material and Methods

Thirty-five healthy ovulatory patients, who were 31.54 ± 1.29 (mean ± SEM) years old, in the follicular phase of the menstrual cycle (between days 7 and 10) participated in the study. Patients were in good health, with no signs of renal or hepatic insufficiency. The protocol was approved by the local Ethics Committee, and written informed consent was obtained from all patients.

Suppositories containing 25, 50 or 100 mg of progesterone (4-pregnene-3,20-dione) powder were prepared as previously described in the literature: progesterone powder (25, 50 or 100 mg), 30% polyethylene glycol 400 USP, 30% polyethylene glycol 1500 USP, 40% polyethylene glycol 4000 USP [8].

One vaginal suppository containing 25, 50 or 100 mg of natural progesterone was applied deep into the vagina by the patient. Blood samples for progesterone assay were drawn immediately before the suppository application (time zero) and at 30 min, 1, 2, 3, 4, 6, 12 and 24 h after insertion of the suppository.

Blood serum was separated by centrifugation and stored at –20°C until the analysis. Serum progesterone was determined by radioimmunoassay using commercial kits from Diagnostic Products Corporation (DPC, USA). The detection limit was 0.05 ng/ml and intra- and interassay coefficients of variation were 7.9 and 5.1%, respectively.

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS 10, Chicago, Ill., USA). Data were expressed as mean ± SEM. Comparisons among groups were performed by ANOVA for repeated measures, followed by the Tukey test. The difference was considered significant at $p < 0.05$.

Results

Table 1 summarizes the baseline data of the participating women. There was no significant difference of age and body mass index (BMI) among the groups.

Figure 1 shows the concentration of serum progesterone in groups treated with 25, 50 and 100 mg of progesterone. The mean baseline value of serum progesterone was similar in all groups ($p = 0.801$). After insertion, natural progesterone absorption through the vaginal mucosa was very rapid, as demonstrated by the increment above the baseline values in the samples obtained 30 min after administration. The progesterone serum concentration reached maximal levels within 2 or 3 h after the insertion of the suppository and it was similar in all the three groups (7.27 ± 2.8 ng/ml; 8.84 ± 3.14 ng/ml, and 9.82 ± 9.8 ng/ml, respectively). During the next 24 h, there was a gradual fall in plasma levels, with half of the maximal concentration being obtained at 12 h for a 100-mg suppository and between 6 and 12 h for the 25- and 50-mg doses. After 24 h, plasma progesterone level was under ovulatory level (max. 2.95 ng/ml with 100 mg). There were no differences among the three groups at any moment of the evaluation.

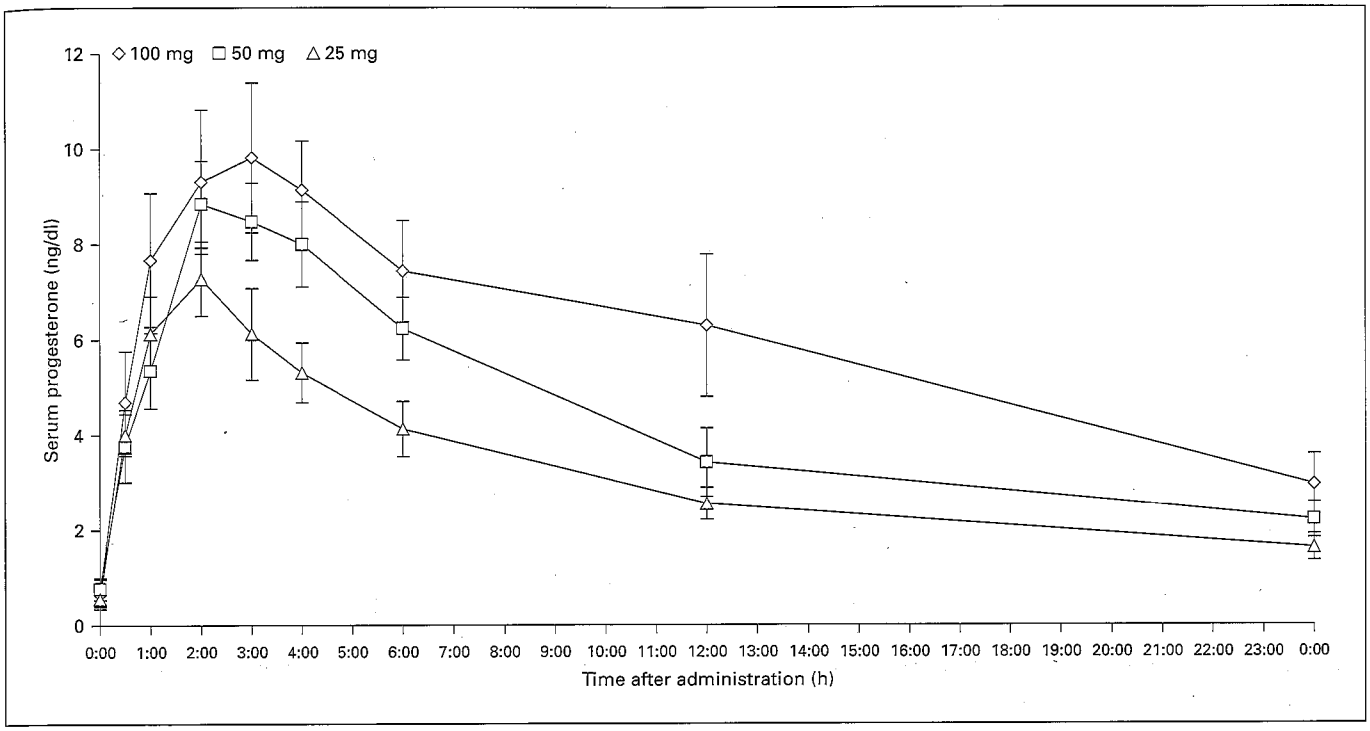

Fig. 1. Serum progesterone levels after vaginal administration of 25, 50 or 100 mg of natural progesterone.

Discussion

The rapid increase in serum progesterone after vaginal administration of progesterone suggests that the vaginal mucosa is a very effective site for absorption and delivery of the hormone. All patients were in the follicular phase of the cycle as demonstrated by the low basal serum progesterone level. Our results cannot be extended to postmenopausal women with vaginal atrophy, because other authors have demonstrated that vaginal absorption was lower in this condition [9, 10].

A wide variation exists in progesterone serum concentration during the menstrual cycle. Concentrations above 3 ng/ml indicate ovulation [11], and in the middle of luteal phase values above 10 ng/ml demonstrate adequate corpus luteum function [12]. Our data showed that ovulatory progesterone concentrations were obtained with all doses of vaginal suppositories.

Similar serum progesterone concentrations were achieved after all the doses. As in our study, Archer et al. [1995] did not observe significant differences of plasma progesterone values among various doses administered vaginally.

Our data suggest that ovulatory progesterone concentration could be achieved with 25, 50 or 100 mg suppository, and these doses should promote endometrial decidualization. Further, in other studies [5] full secretory transformation of the endometrium has been produced by serum progesterone levels of 1–3 ng/ml after vaginal administration, but not after intramuscular or nasal delivery [13]. Because of the lower half-life ($T_{1/2}$) obtained with the 25- and 50-mg suppositories, the drug could be administered 3 times a day. With the 100-mg suppository middle luteal phase progesterone levels could be reached with only twice daily applications.

Early studies [13] showed that the endometrial levels of progesterone obtained after intravaginal administration are higher than those seen after dosing by the oral or intramuscular routes. The endometrial progesterone concentrations were not determined in this study, but we suppose that an adequate tissue concentration should be achieved with a 25-mg suppository, with minimal progesterone systemic side effects.

Conclusion

Exogenous natural progesterone supplementation is an integral part of modern infertility treatment (luteal phase support), and the use in hormone replacement therapy should be encouraged. A very low dose of vaginal progesterone may protect against endometrial hyperplasia, with relatively low serum levels, minimizing the adverse metabolic effects associated with oral progestins. In summary, our study demonstrated that vaginally administered progesterone could reach ovulatory and luteal phase levels. The progesterone regimen for adequate endometrial protection and in IVF programs remains to be studied.

References

1 Posaci C, Smitz J, Camus M, Osmanagaoglu K, Devroey P: Progesterone for the luteal support of assisted reproductive technologies: clinical options. Hum Reprod 2000;15(suppl 1):129–148.

2 Hendrickx AG, Korte R, Leuschner F, Neumann BW, Prahalada S, Poggel A, Binkerd PE, Gunzel P: Embryotoxicity of sex steroidal hormone combinations in nonhuman primates. I. Norethisterone acetate + ethinylestradiol and progesterone + estradiol benzoate *(Macaca mulatta, Macaca fascicularis,* and *Papio cynocephalus)*. Teratology 1987;35:119–127.

3 Bourgain C, Devroey P, Van Waesberghe L, Smitz J, Van Steirteghem AC: Effects of natural progesterone on the morphology of the endometrium in patients with primary ovarian failure. Hum Reprod 1990;5:537–543.

4 Nahoul K, Dehennin L, Jondet M, Roger M: Profiles of plasma estrogens, progesterone and their metabolites after oral or vaginal administration of estradiol or progesterone. Maturitas 1993;16:185–202.

5 Pouly JL, Bassil S, Frydman R, Hedon B, Nicollet B, Prada Y, Antoine JM, Zambrano R, Donnez J: Luteal support after in-vitro fertilization: Crinone 8%, a sustained release vaginal progesterone gel, versus Utrogestan, an oral micronized progesterone. Hum Reprod 1996;11:2085–2089.

6 Bolaji II, Mortimer G, Grimes H, Tallon DF, O'Dwyer E, Fottrell PF: Clinical evaluation of near-continuous oral micronized progesterone therapy in estrogenized postmenopausal women. Gynecol Endocrinol 1996;10:41–47.

7 de Ziegler D and Fanchin R: Progesterone and progestins: Applications in gynecology. Steroids 2000;65:671–679.

8 Roffe BD, Zimmer RA, Derewicz HJ: Preparation of progesterone suppositories. Am J Hosp Pharm 1977;34:1344–1346.

9 Pschera H, Hjerpe A, Carlstrom K: Influence of the maturity of the vaginal epithelium upon the absorption of vaginally administered estradiol-17 beta and progesterone in postmenopausal women. Gynecol Obstet Invest 1989;27:204–207.

10 Villanueva B, Casper RF, Yen SS: Intravaginal administration of progesterone: Enhanced absorption after estrogen treatment. Fertil Steril 1981;35:433–437.

11 Filicori M, Butler JP, Crowley WF Jr: Neuroendocrine regulation of the corpus luteum in the human: Evidence for pulsatile progesterone secretion. J Clin Invest 1984;73:1638–1647.

12 Hull MG, Savage PE, Bromham DR, Ismail AA, Morris AF: The value of a single serum progesterone measurement in the midluteal phase as a criterion of a potentially fertile cycle ('ovulation') derived form treated and untreated conception cycles. Fertil Steril 1982;37:355–360.

13 Miles RA, Paulson RJ, Lobo RA, Press MF, Dahmoush L, Sauer MV: Pharmacokinetics and endometrial tissue levels of progesterone after administration by intramuscular and vaginal routes: A comparative study. Fertil Steril 1994;62:485–490.