

Pharmacokinetics of natural progesterone administered in the form of a vaginal tablet

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Our study was conducted to assess the pharmacokinetics of natural progesterone administered in the novel formula of an effervescent vaginal tablet. Fifty post-menopausal women, with a median age of 43.5 years (range 28–55), volunteered to participate in the research. All women discontinued their hormonal replacement therapy 1 month prior to the study. The pharmacokinetics of 50 and 100 mg of progesterone administered as a vaginal tablet were evaluated. After the initial administration of 50 mg or 100 mg, a mean serum C_{max} of 20.43 ± 8.01 nmol/l and 31.61 ± 12.62 nmol/l ($P < 0.0004$) was reached at a T_{max} of 6.1 ± 2.63 and 6.4 ± 3.35 h respectively. The terminal half-life was 13.18 ± 1.3 and 13.7 ± 1.05 h respectively. Continuous use of the 100-mg tablet resulted in a mean serum progesterone concentration of 26.08 ± 13.96 nmol/l and 21.42 ± 16.32 nmol/l after 14 and 30 days respectively. Women >40 years were found to have a significantly lower T_{max} compared to younger women ($P = 0.02$). The continuous use of vaginal progesterone did not influence the hormonal, liver or lipid profiles evaluated. Only three (6%) women suffered from mild vaginal irritation. Natural progesterone given as a vaginal tablet is well tolerated, safe and an easily administered treatment. Even in a non-oestrogenized vagina the absorption was efficient and the 100 mg dosage resulted in adequate serum progesterone concentrations.

Key words: assisted reproductive technology/pharmacokinetics/progesterone/vaginal tablets

Introduction

Since its discovery in the 1950s, synthetic oral progesterone has been used for a variety of gynaecological conditions. However, androgenic activity inherent in the synthetic compound precludes its liberal use in assisted reproductive technology because of the threat of teratogenic effects. Furthermore, synthetic progesterone used in hormonal replacement therapy (HRT) may partially reverse the oestrogenic benefits on the

cardiovascular system and lipoprotein metabolism (Fahraeus *et al.*, 1983; Ottosson *et al.*, 1985; Knopp, 1988; Crook *et al.*, 1992; Lobo, 1992).

Natural progesterone is devoid of any androgenic activity that might compromise lipoprotein metabolism or induce teratogenicity. Moreover, it probably has a direct beneficial effect on blood vessels (Jiang *et al.*, 1992). The major problem with natural progesterone is its route of administration. Oral intake is hampered by rapid and extensive intestinal and liver metabolism leading to poorly sustained serum concentrations and low bioavailability (Nillus and Johanson, 1971; Adlercreutz and Martin, 1980; Whitehead *et al.*, 1980; Ottosson *et al.*, 1984; Padwick *et al.*, 1986; Chakmakjian and Zachariah, 1987; Arafat *et al.*, 1988; Nahoul *et al.*, 1993). Injection *i.m.* assures reliable absorption, but is related to low compliance. It is painful, can cause local irritation and cold abscesses (Devroey *et al.*, 1989), and must be administered by trained medical personnel. Thus the vaginal route has become the most established way in which to deliver natural progesterone. The progesterone is easily administered and avoids liver first-pass metabolism, and the vagina has a large potential for absorption. Many vaginal formulations have been assayed, mostly as suppositories (Price *et al.*, 1983; Norman *et al.*, 1991; Archer *et al.*, 1995; Pasquale *et al.*, 1997), gelatin capsules (Devroey *et al.*, 1989; Smitz *et al.*, 1992; Miles *et al.*, 1994), and recently as bio-adhesive gels (Fanchin *et al.*, 1997; Ross *et al.*, 1997). Although the suppositories are easily inserted, they melt at body temperature and lead to disturbing vaginal discharge. Oral gelatin capsules containing micronized progesterone have also been used vaginally (Devroey *et al.*, 1989; Smitz *et al.*, 1992; Miles *et al.*, 1994), but insertion of a small capsule high into the vagina is difficult and large doses of 600–800 mg are needed to achieve adequate plasma concentration (Bourgain *et al.*, 1990; Smitz *et al.*, 1992; Miles *et al.*, 1994).

The use of a vaginal tablet containing progesterone has been reported in dogs (Fulper *et al.*, 1987), but has not been pharmacologically evaluated in humans. In the present study we examined the pharmacokinetics of natural progesterone administered in the form of vaginal tablets to non-oestrogen-primed post-menopausal women. Dosages of 50 and 100 mg were used to determine single-dose pharmacokinetics. The effect of continuous use on hormonal, chemical, and lipid profiles were evaluated.

Materials and methods

Patients

Fifty healthy, post-menopausal women with intact uteri were enrolled in the study. Thirty-nine women had suffered from premature meno-

pause and were treated in our oocyte donation programme, and 11 were truly post-menopausal. The participants underwent thorough medical history, physical and gynaecological examinations, including Papanicolaou smear and transvaginal sonography. All were using HRT and were instructed to cease the HRT 1 month prior to the study. All subjects volunteered to participate in the study and provided their written, informed consent.

Study design

The study was divided into two parts: The first was designed to evaluate the pharmacokinetics of natural progesterone administered by a single vaginal tablet. Micronized progesterone (Upjohn Company, Kalamazoo, MI, USA) was condensed into a 1.2 g effervescent tablet formulation using a direct compaction method (Floris Company Ltd., Gush Segev, Israel). The tablets contained either 50 or 100 mg of micronized progesterone. At 8 a.m. (day 0) in a fasting state an intravenous indwelling catheter was introduced into the cubital vein. Blood was drawn for baseline hormonal [progesterone, oestradiol, follicle-stimulating hormone (FSH), luteinizing hormone (LH), dehydroepiandrosterone sulphate (DHEAS), cortisol and aldosterone], liver [bilirubin, alkaline phosphatase, serum glutamic oxaloacetic transaminase (SGOT)] and lipid [cholesterol, triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL), very low density lipoprotein (VLDL)] profiles. The women were then instructed to self-administer the progesterone vaginal tablet using a plastic applicator and lie down for 20 min. Repeat blood samples for progesterone concentration were withdrawn $\frac{1}{2}$, 1, 2, 4, 6, 8, 10, 12 and 24 h after the vaginal insertion. Blood was allowed to clot at room temperature for 1 h, after which the serum was separated by centrifugation and stored at -20°C until analysis.

The second part of the study was designed to evaluate clinical use of the drug. The women were instructed to insert progesterone vaginal tablets containing the same dose as that on day 0, twice daily starting on day 1, and to recline for 20 min after each insertion. Blood for the same assays as in the baseline tests was drawn on days 14 and 30, in the morning before progesterone administration and in a fasting state. The women were instructed to observe and record every unusual feeling or side-effect.

Hormonal assays

Immulate enzyme immunoassay (Diagnostic Products Corporation, Los Angeles, CA) was used to measure plasma progesterone (SI conversion factor 3.18; sensitivity 0.2 ng/ml (0.6 nmol/l, inter- and intra-assay coefficients of variation precision <10%), oestradiol (SI conversion factor 3.67; sensitivity 12 pg/ml (44 pmol/l, inter- and intra-assay coefficients of variation precision <10%), DHEAS (SI conversion factor 0.02714; sensitivity 2 $\mu\text{g/ml}$ (0.054 $\mu\text{mol/l}$, inter- and intra-assay coefficients of variation precision <10%). Cortisol was measured using the Access immunoassay (Sanofi Diagnostics Pasteur, Paris, France). This assay has a sensitivity of 0.4 mg/dl with inter- and intra-assay coefficients of variation precision <10%. Aldosterone was measured by a radioimmunoassay kit (Diagnostic Products Corporation, Los Angeles, CA, USA). This assay has a sensitivity of 16 pg/ml with inter- and intra-assay coefficients of variation precision <10%. Luteinizing hormone and FSH were measured by enzyme-linked immunosorbent assay (ELISA) Enzyme-Test kit (Boehringer Mannheim Immunodiagnosics, Sussex, UK) which has a sensitivity of 0.5 mIU/ml for LH and FSH with inter- and intra-assay coefficients of variation precision <10%.

Statistical analysis

The area under the curve (AUC) was calculated by the trapezoidal rule. Concentrations up to 24 h were considered. The pharmacokinetic

Table I. Baseline details of the study group

	Progesterone dose (mg)		
	50 (<i>n</i> = 20)	100 (<i>n</i> = 30)	All (<i>n</i> = 50)
Median age (years) (range)	43 \pm 6.1 (28–53)	43.2 \pm 7.9 (28–55)	43.3 \pm 7.2 (28–55)
Height (cm)	161.3 \pm 8.6	161.6 \pm 5.7	161.5 \pm 6.9
Weight (kg)	67.1 \pm 11.5	62.8 \pm 13.1	64.5 \pm 12.5
BMI (kg/m ²)	25.9 \pm 4.2	24.0 \pm 4.4	24.8 \pm 4.4

Data are expressed as mean \pm SD unless otherwise specified. Body mass index (BMI) was calculated as weight (in kg) divided by the square of height (in metres).

parameters calculated from the concentration curve were compared between the two study groups by the Wilcoxon test and by analysis of variance (ANOVA) models. The significance of changes of the other laboratory measurements from baseline values was determined by the paired *t*-test.

Results

Fifty post-menopausal women volunteered to participate in the study: 20 were allocated vaginal tablets containing 50 mg progesterone, and the 100 mg dosage was prescribed for 30 women. Table I summarizes the baseline details of the participating women. There was no significant difference between the two dose groups in age, weight, height or body mass index (BMI). The median age, mean height, mean weight and the mean BMI of the study group were 43.3 ± 7.2 years (range 28–55), 161.5 ± 6.9 cm, 64.5 ± 12.5 kg, and 24.8 ± 4.4 kg/m² respectively.

The progesterone-containing vaginal tablet was well tolerated by all the women. The tablets were easily administered and none complained of significant vaginal losses. All participating women experienced some degree of hot flushes after discontinuing their regular HRT. The menopausal symptoms did not worsen during the study period. No subjects withdrew from the study because of side effects or adverse reaction to progesterone. Three women (6%) complained of mild vulvovaginal irritation related to moniliasis. The infection was relieved by antimycotic treatment. One woman developed urinary tract infection that was successfully treated with antibiotics. No sleepiness, drowsiness, dizziness, headaches or breakthrough vaginal bleeding were reported.

Single dose pharmacokinetics

A single vaginal application of a 50 mg progesterone tablet resulted in the rapid increase of plasma progesterone concentration (Figure 1). Mean peak plasma progesterone concentrations (T_{max}) occurred after 6.1 ± 2.63 h, with a mean elimination half-life ($T_{1/2}$) of 13.18 ± 1.3 h (Table II). The 100 mg dose exhibited similar kinetics (Figure 1), with a T_{max} of 6.4 ± 3.35 h and $T_{1/2}$ of 13.7 ± 1.05 h (Table II). A significantly higher mean maximal serum concentration (C_{max}) of 31.61 ± 12.62 nmol/l was achieved by the 100 mg dose, compared to 20.43 ± 8.01 nmol/l achieved by the 50 mg progesterone vaginal tablet ($P = 0.0004$). The 100 mg dose also resulted in a significantly higher mean AUC of 247.61 ± 123.04 nmol/

h/l, compared to 154.15 ± 60.31 nmol/h/l in the 50 mg dose ($P = 0.001$).

In order to evaluate the influence of age on vaginal progesterone absorption, the different pharmacokinetic parameters were separately analysed in women ≤ 40 years, compared to women >40 years (Table III). The statistical calculations included age as a covariant in the ANOVA models. Age contribution to the model was examined in two ways: first as a continuous variable, and then as dichotomous variables (≤ 40 years and >40 years). Significantly lower T_{max} was found in women >40 years, compared to the younger age group. This finding was consistent in the 50 mg dose group (5.47 ± 2.33 versus 8.0 ± 2.83 h; $P = 0.02$) and in the 100 mg dose group (5.89 ± 3.25 versus 7.27 ± 3.5 h; $P = 0.02$) (Figure 2). The other parameters were not influenced by age (Table III). Furthermore,

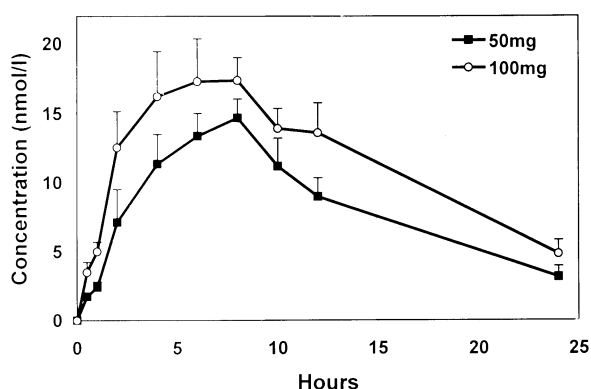


Figure 1. Plasma progesterone concentrations (mean \pm SD) after administration of progesterone-containing vaginal tablets. Women received 50 mg ($n = 20$) or 100 mg ($n = 30$).

Table II. Pharmacokinetic parameters of progesterone administered by vaginal tablets

	Progesterone dose (mg)	
	50 ($n = 20$)	100 ($n = 30$)
T_{max} (h)	6.1 ± 2.63	6.4 ± 3.35
$T_{1/2}$ (h)	13.18 ± 1.3	13.7 ± 1.05
C_{max} (nmol/l)	20.43 ± 8.01	31.61 ± 12.62^a
AUC (nmol/h/l)	154.15 ± 60.31	247.61 ± 123.04^b

Values are mean \pm SD; $^aP = 0.0004$; $^bP = 0.001$.

Table III. Pharmacokinetic parameters of vaginal progesterone absorption in relation to age

	Progesterone dose (mg)			
	50		100	
	≤ 40 years ($n = 5$)	>40 years ($n = 15$)	≤ 40 years ($n = 12$)	>40 years ($n = 18$)
T_{max} (h)	8.0 ± 2.83	5.47 ± 2.33^a	7.27 ± 3.5	5.89 ± 3.25^a
$T_{1/2}$ (h)	14.7 ± 3.77	11.94 ± 3.87	14.61 ± 9.1	12.73 ± 4.09
C_{max} (nmol/l) ^b	20.24 ± 6.11	20.51 ± 8.75	32.05 ± 11.9	31.34 ± 13.4
AUC (nmol/h/l) ^c	189.3 ± 40.04	142.44 ± 62.37	296.6 ± 13	217.6 ± 106.2

Values are means \pm SD.

$^aP = 0.02$, statistical significance for age difference.

$^bP = 0.0004$, statistical significance for dose difference but not for age.

$^cP = 0.001$, statistical significance for dose difference but not for age.

no significant difference in pharmacokinetic behaviour was found in relation to weight, height or BMI indices.

Continuous use

After 14 and 30 days of continuous application twice daily, the serum progesterone concentrations were significantly higher compared to baseline values on day 0 (Table IV). No significant difference in serum progesterone concentration was found between days 14 and 30, in either dose group, although, as expected, higher concentrations of 26.08 ± 13.96 nmol/l and 21.42 ± 16.32 nmol/l respectively were achieved with the 100 mg progesterone vaginal tablet, compared to 17.48 ± 9.8 nmol/l on day 14 and 17.38 ± 14.39 nmol/l on day 30 for the 50 mg dose (Table IV).

No statistically significant difference in plasma concentrations of FSH, LH, oestradiol, cortisol, DHEAS, and aldosterone were observed in the study groups between baseline values and after chronic administration. Comparable results were obtained for plasma concentrations of SGOT, alkaline phosphatase, cholesterol, triglycerides, HDL, LDL and VLDL, indicating that continuous administration of progesterone by way of a vaginal tablet did not influence liver enzymes or lipid profiles.

Discussion

Progesterone support during the luteal phase and early pregnancy is mandatory in in-vitro fertilization (IVF) cycles down-regulated with gonadotrophin-releasing hormone analogues (GnRH-a) (Smitz *et al.*, 1987, 1988), and in women treated for oocyte donation (Sauer *et al.*, 1992; Borini *et al.*, 1995). At times, such supplementation should be continued for several weeks. In recent years it has been established that the vaginal route is preferable for natural progesterone administration. However, the most reliable formulation to meet the patient's compliance as well as therapeutic efficacy, is still under investigation.

The present study defines the pharmacokinetics of micronized natural progesterone administered by the novel formulation of a vaginal tablet. Non-oestrogen-primed postmenopausal women were chosen in order to avoid confusion with endogenous progesterone secretion and oestrogen influ-

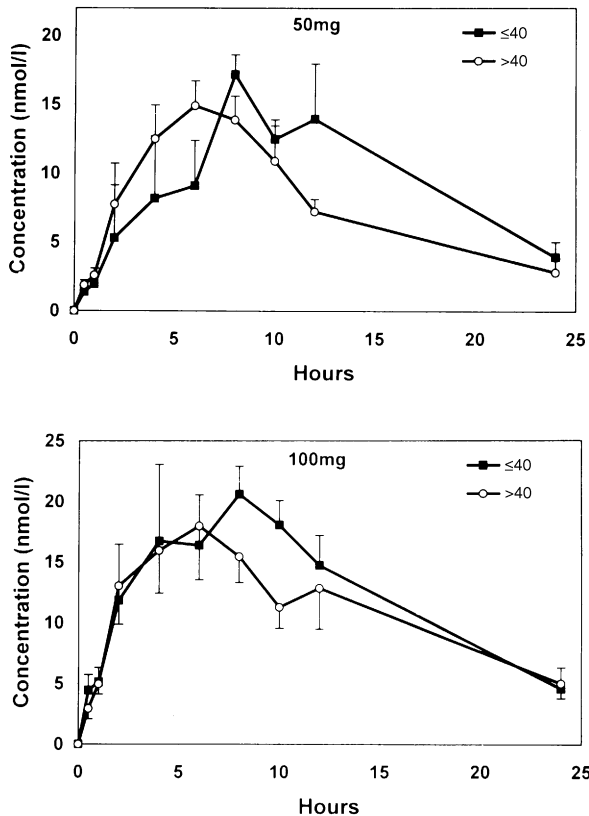


Figure 2. Comparison of plasma progesterone concentrations (mean \pm SD) after administration of progesterone-containing vaginal tablets in women 40 years and younger and in women older than 40 years. Evaluation for 50 mg (upper) and 100 mg (lower) vaginal tablets.

ence on vaginal mucosa absorption (Villanueva *et al.*, 1981). Both the 50 mg and 100 mg vaginal tablets demonstrated similar pharmacokinetic patterns (Figure 1) of rapid absorption, reaching a T_{max} within 6 h, with a $T_{1/2}$ of about 13 h. These results indicate that the progesterone vaginal tablet should be administered twice daily. Indeed, plasma progesterone concentration after 14 and 30 days of treatment revealed sustained concentrations with this twice-daily regimen (Table IV).

A wide variation exists in progesterone serum concentrations during the menstrual cycle. It is accepted that concentrations above 3.3 ng/ml (10.5 nmol/l, SI conversion factor 3.18) indicate that ovulation has occurred (Israel *et al.*, 1972), while mid-luteal phase values of 10 ng/ml (31.8 nmol/l) and above demonstrate adequate corpus luteum function (Rosenfeld *et al.*, 1980). The current data show that similar concentrations were achieved with the 100 mg progesterone vaginal tablet, with a C_{max} of 31.61 ± 12.62 nmol/l (9.94 ± 3.96 ng/ml) and progesterone concentrations of 26.08 ± 13.96 nmol/l (8.4 ± 4.4 ng/ml) after receiving 100 mg b.d. for 14 days. The wide standard deviation probably reflects different times of progesterone insertion the evening prior to the clinic visit. These serum progesterone values were obtained without vaginal priming by oestrogen. It was previously reported that oestrogen therapy markedly increases vaginal progesterone absorption (Villanueva *et al.*, 1981). Shushan *et al.* (1994) have shown

Table IV. Serum progesterone concentrations at baseline and after continuous vaginal progesterone administration

Progesterone (nmol/l)	Progesterone dose (mg)	
	50 ($n = 20$)	100 ($n = 30$)
Day 0 ^a	1.05 \pm 0.7	3.0 \pm 2.4
Day 14 ^a	17.48 \pm 9.8 ^b	26.08 \pm 13.96 ^b
Day 30 ^a	17.38 \pm 14.39	21.42 \pm 16.32

^a $P = 0.0001$, significant difference between progesterone baseline values on day 0 compared to day 14 and day 30; ^b $P = 0.02$.

that a combined vaginal tablet containing 6 mg of oestradiol and 50 mg of progesterone produced by the same manufacturer as the tablets in the present study achieved midluteal progesterone concentrations of 21.6 ± 2.5 ng/ml (68.6 ± 7.95 nmol/l) with a twice-daily treatment regimen. Endometrial biopsies showed in-phase endometrial histology in eight of nine women (Shushan *et al.*, 1994). No endometrial biopsies were obtained in our study, since only progesterone was evaluated and transvaginal sonography at the completion of the 30 days of treatment revealed only a thin (2–3 mm) endometrium in all women.

Furthermore, Miles *et al.* (1994) described a uterine 'first pass' effect induced by vaginal progesterone administration. The authors reported a higher concentration of progesterone in the endometrium (11.5 ± 2.6 ng/ml) after continual administration vaginally for 6 days, compared to i.m. treatment (1.4 ± 0.4 ng/ml), in normal ovulatory women. Interestingly, after the vaginal progesterone application, the endometrial and plasma progesterone concentrations were similar (11.5 ± 2.6 ng/ml, and 11.9 ± 1.2 ng/ml respectively). These results may suggest that adequate endometrial concentrations can be achieved even with low doses of progesterone.

To date, vaginal tablets were used to deliver antimycotic or antibacterial drugs. To the best of our knowledge, this is the first report of pharmacokinetic evaluation of a progesterone-containing vaginal tablet in humans. The advantage of the vaginal tablet is that it absorbs the vaginal secretions and disintegrates into an adhesive powder that adheres to the vaginal epithelium, thus facilitating sustained release. This effect is also evident from the results obtained in women from different age groups. It appears that women >40 years demonstrated enhanced absorption of vaginal progesterone (5.47 ± 2.33 h for the 50 mg and 5.89 ± 3.25 h for the 100 mg), compared to women ≤ 40 years (8.0 ± 2.83 h and 7.27 ± 3.5 h for the 50 and 100 mg tablets respectively) (Table III). These data are probably explained by thinner and more atrophic vaginal mucosa in older women. However, no significant difference was observed in the C_{max} or AUC between the age groups (Table III), indicating that the tablet was fully absorbed.

Other advantages are related mostly to patient compliance. Vaginal tablets are easily administered by the woman herself. There is no messy discharge as is sometimes seen with vaginal suppositories or creams. Only three women (6%) experienced minimal vaginitis during the treatment, and none withdrew from the study due to local vulvovaginal irritation. The vaginal

tablet should be inserted only twice daily. This is a convenient schedule also for working women who can insert the tablet in the morning before going to work and in the evening when they return, compared to the vaginally used oral progesterone gelatin capsule that needs to be inserted 3 or 4 times per day (Devroey *et al.*, 1989; Smitz *et al.*, 1992; Miles *et al.*, 1994).

The continuous use of the vaginal tablet was well tolerated with no influence on liver enzymes or lipid profiles. This is probably a result of direct absorption of progesterone from the vaginal mucosa into the blood stream, bypassing the liver. Also, the hormonal concentrations of LH, FSH, cortisol, and aldosterone were not affected by the progesterone treatment, since no significant difference from baseline concentrations was observed.

In conclusion, natural micronized progesterone given as an effervescent vaginal tablet, is a well-tolerated and safe product. Reliable release and absorption were obtained with both 50 mg and 100 mg vaginal tablets. Adequate luteal plasma concentrations were achieved with the 100-mg dose even in non-oestrogen primed women. The easy administration and lack of side effects assure good patient compliance. Further pharmacokinetic studies are currently being conducted to evaluate oestradiol and progesterone concentrations after the combination of oestradiol and vaginal tablets, as well as their effect on endometrial histology.

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