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Pharmacokinetics of the progesterone-containing vaginal tablet and its use in assisted reproduction

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Abstract

Natural progesterone, which is devoid of androgenic activity, is widely used in assisted reproduction for luteal and pregnancy support. The vaginal route has become the most established way to deliver natural progesterone because it is easily administered, avoids liver first-pass metabolism, and has no systemic side-effects. The vagina has a large potential for absorption, and through the 'uterine first-pass effect' vaginal administration results in higher uterine progesterone concentrations. We have investigated the pharmacokinetics of natural progesterone in the form of a vaginal tablet. A single dose of 100 mg resulted in a mean C_{max} of 31.53 ± 9.15 nmol/l with a T_{max} of 6.92 ± 3.12 h. The terminal half-life was 16.39 ± 5.25 h. The pharmacokinetic data are discussed in relation to dose, age, and estrogen priming. Single-dose pharmacokinetics of 100 mg of progesterone vaginal tablets and gelatin capsules were evaluated over 24 h. Results indicated a similar mean T_{max} of 6.92 ± 3.12 and 6.23 ± 6.57 h, respectively. However, a significantly higher C_{max} was achieved by the vaginal tablet (31.95 ± 9.15 and 23.85 ± 9.57 nmol/l, respectively, $P < 0.05$). Continuous use of vaginal progesterone did not influence the hormonal, liver, or lipid profiles evaluated. There was no case of endometrial hyperplasia. The vaginal tablet was found to be well-tolerated, safe, and easily administered. In conclusion, progesterone-containing vaginal tablets have good pharmacokinetic properties and should be used for progesterone supplementation in IVF.

Keywords: Assisted reproductive technology; Gelatin capsule; Pharmacokinetics; Progesterone; Vaginal tablet

1. Introduction

Synthetic oral progesterone has been widely used for a variety of gynecological problems, such as endometrial hyperplasia, dysfunctional uterine bleeding, endometriosis, premenstrual syndrome, and luteal phase defect (LPD). Progesterone supplementation is also mandatory in gonadotropin releasing hormone analog (GnRH-a) down-regulated in vitro fertilization (IVF) cycles and as part of the endometrial preparation in oocyte donation programs. However, androgenic activity, inherent in the synthetic compounds, especially those of the 19-nortestosterone configuration, limit their use in infertility treatment and for pregnancy support due to possible teratogenic effects [1].

Natural progesterone is devoid of any androgenic activity and is thus extensively used in assisted reproduction, sometimes for long periods of time. The major problem with natural progesterone is its route of administration. Oral intake is the most convenient. However, rapid and extensive intestinal metabolism prevents adequate absorption [1–10]. Moreover, liver metabolism results in metabolites that induce side effects, such as drowsiness and sedation [3]. Intramuscular (i.m.) injection of natural progesterone assures reliable absorption but is related to poor compliance. Because the injection is oil-based, it is painful and can cause local irritation and cold abscesses [11]. Furthermore, it must be administered by trained medical personnel.

For these reasons, the vaginal route has become the most effective way to deliver natural progesterone. The vagina has good absorption potential, and the drug is administered easily and effectively via the vaginal route by the patient. This mode of administration avoids liver first-pass metabolism. Recently, vaginal drug delivery has gained further interest due to investigations showing the existence of 'uterine first pass effect' [12–16]. According to this concept, drugs administered through the vaginal route are transmitted primarily to the uterus, where they achieve higher tissue concentrations than if administered orally or by i.m. injections [12].

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Many vaginal formulations have been assessed, mostly as suppositories, gelatin capsules, and lately as a bioadhesive gel. 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. However, insertion of a small capsule high in the vagina is difficult, and large doses of 600 to 800 mg per day are needed to achieve adequate plasma concentrations, as well as secretory endometrial histology [17–19].

The lack of a proper vaginally designed formulation has resulted in further search for an effective means of vaginal drug delivery. Vaginal tablets containing natural micronized progesterone have been used for almost a decade now by several IVF centers in Israel for progesterone supplementation. 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 and facilitates sustained release [20]. In this article we will review several studies evaluating the pharmacokinetic properties and physiological aspects of progesterone-containing vaginal tablets.

2. Pharmacokinetics of progesterone-containing vaginal tablets

2.1. Experimental

Fifty healthy postmenopausal women with intact uteri volunteered to participate in the study. The median age was 43 years (range 28–55 years). Thirty-nine women suffered from premature menopause and were treated in our oocyte donation program. Eleven women were actually postmenopausal. All women were using hormonal replacement therapy (HRT) and were instructed to stop the treatment one month before the study.

The study was divided into two parts: The first was designed to determine single-dose pharmacokinetics of the vaginal progesterone tablets. Micronized progesterone (Upjohn Company, Kalamazoo, MI, USA) was condensed into a 1.2 g effervescent tablet formulation using a direct compaction method (Endometrin, Floris Company Ltd., Gush Segev, Israel). Study design, treatment protocol, blood test schedules, as well as hormonal and biochemical assays, have been described elsewhere [20]. At 8 a.m. (day 0), when subjects were in a fasting state, blood was drawn for baseline progesterone level as well as for other hormonal, biochemical, and lipid tests. The women were then instructed to insert a vaginal tablet containing either 50 or 100 mg of progesterone using a plastic applicator and to lie down for 20 min. Repeat blood samples for progesterone concentration were withdrawn ½, 1, 2, 4, 6, 8, 10, 12, and 24 h after the vaginal insertion. The second part of the study was designed to evaluate clinical use of the drug. The women were instructed to insert the vaginal tablets containing the same amount of progesterone as on day 0 twice daily starting on day 1. Blood for progesterone concentration and for other hormonal, chemical, and lipid tests were drawn on days 14 and 30 on the morning before the tablet was administered.

Table 1
Pharmacokinetic parameters of progesterone administered by vaginal tablet

	Progesterone dose	
	50 mg ($n = 20$)	100 mg ($n = 30$)
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[a]

Values are means ± SD.
[a] $P < 0.001$.

2.2. Results

Twenty women received vaginal tablets containing 50 mg of progesterone, and 30 women were assigned to the 100 mg group. There was no significant difference between the two dose groups in relation to age, weight, height, or body mass index.

Both the 50 and 100 mg vaginal tablets demonstrated similar pharmacokinetic patterns of rapid absorption, reaching a mean peak plasma progesterone concentration (T_{max}) within 6 h, with a mean elimination half-life ($T_{1/2}$) of about 13 h (Table 1). A significantly higher mean maximal serum concentration (C_{max}) of 31.61 ± 12.62 nmol/l was achieved by the 100 mg dose, as compared to 20.43 ± 8.01 nmol/l achieved by the 50 mg progesterone-containing vaginal tablet. The 100 mg dose also resulted in a significantly higher mean area under the curve (AUC) compared to the 50 mg dose.

The different pharmacokinetic parameters were also evaluated by age. Interestingly, a significantly lower T_{max} was found in women older than 40 years compared to women younger than 40 years (5.47 ± 2.33 and 8.0 ± 2.83 h, respectively, for the 50 mg dose and 5.89 ± 3.25 and 7.27 ± 3.5 h, respectively, for the 100 mg dose group). The other pharmacokinetic parameters were not significantly influenced by age.

Serum progesterone levels after 14 and 30 days of twice daily continuous application were significantly higher compared to baseline values on day 0. No significant difference in serum progesterone concentration was found between days 14 and 30 in each dose group. However, as expected, higher levels of 26.08 ± 13.96 on day 14 and 21.42 ± 16.32 nmol/l on day 30 were achieved with the 100 mg dose compared to 17.48 ± 9.8 on day 14 and 17.38 ± 14.39 nmol/l on day 30 for the 50 mg dose.

No statistically significant difference in plasma hormonal levels (LH, FSH, estradiol, cortisol, DHEAS, and aldosterone), liver function tests, or lipid profiles were observed in the two dose groups between baseline values and after continuous administration for 30 days.

Table 2
Pharmacokinetic parameters of progesterone administered by vaginal tablet in non-estrogen- and in estrogen-primed women

	Progesterone only	Estrogen + progesterone
T_{max} (h)	5.8 ± 2.7	9.95 ± 7.6[a]
$T_{1/2}$ (h)	14.4 ± 4.7	21.2 ± 12.4
C_{max} (nmol/l)	34.0 ± 12.8	39.1 ± 13.2
AUC (nmol/h/l)	278.7 ± 143.4	423.6 ± 223.8[b]

Values are means ± SD.
[a] $P < 0.05$.
[b] $P < 0.02$.

Table 3
Pharmacokinetic parameters for single-dose progesterone administered as a vaginal tablet or vaginal gelatin capsule

	Vaginal tablet	Gelatin capsule
T_{max} (h)	6.92 ± 3.12	6.23 ± 6.57[a]
$T_{1/2}$ (h)	16.39 ± 5.25	22.08 ± 16.5
C_{max} (nmol/l)	31.53 ± 9.15	23.85 ± 9.57[b]
AUC (nmol/h/l)	379.99 ± 137.07	325.89 ± 167.78

Values are means ± SD.
[a] Statistically significant difference of variance, $P < 0.02$.
[b] $P < 0.05$.

3. Estrogen influence on vaginal progesterone absorption

3.1. Experimental

The pharmacokinetic profile of vaginal progesterone absorption was compared in non-estrogen-primed and in estrogen-primed postmenopausal women. Twenty postmenopausal women with a median age of 48 years (range 38–55 years) participated in the study. All discontinued their HRT one-month before the study. Primarily, single-dose pharmacokinetic studies of 100 mg of progesterone in the form of a vaginal tablet (Endometrin, Floris Company Ltd, Gush Segev, Israel) were conducted over 24 h (as described in Section 2). The women were then instructed to administer a vaginal tablet containing 3 mg of ethinyl estradiol (Schering AG/Berlin Germany) once a day for 2 weeks. After this estrogen-priming treatment, we evaluated again single-dose pharmacokinetic parameters of the 100 mg progesterone-containing vaginal tablet over 24 h.

3.2. Results

As expected, estrogen priming resulted in increased vaginal progesterone absorption (Table 2). A higher C_{max} and a significantly higher AUC were achieved after estrogen treatment (39.1 ± 13.2 nmol/l and 423.6 ± 223.8 nmol/h/l after estrogen priming versus 34.0 ± 12.8 nmol/l and 278.7 ± 143.4 nmol/h/l after progesterone alone, respectively). Interestingly, estrogen priming resulted in slow vaginal absorption. A significantly prolonged T_{max} of 9.95 ± 7.6 h was observed after vaginal estrogen treatment compared to 5.8 ± 2.7 h for naïve progesterone absorption. Similarly, the $T_{1/2}$ was also longer (21.2 ± 12.4 h versus 14.4 ± 4.7 h, respectively).

4. Comparative bioavailability of progesterone-containing vaginal formulations

4.1. Experimental

In this study, our group compared the pharmacokinetic parameters and bioavailability of two progesterone-containing vaginal formulations: a gelatin capsule (Utrogestan, Basins–Iscovesco, Paris, France) and a vaginal tablet (Endometrin, Floris Company Ltd., Gush Segev, Israel).

Thirteen postmenopausal women with a median age of 53 years (range 42 to 57 years) and intact uteri volunteered to participate in the study. All were using HRT and were instructed to discontinue the treatment 2 weeks before the study. The participants received 4 mg of oral ethinyl estradiol (Estrofem, Novo–Nordisk, Denmark) for 14 days. Single-dose pharmacokinetics of 100 mg of the two formulations were then evaluated [21].

4.2. Results

Vaginal application of either drug resulted in a rapid increase in plasma progesterone concentrations within 2.5 to 3 h. However, the mean progesterone concentrations after administration of the progesterone gelatin capsule reached a plateau after 12 h with almost steady state concentrations thereafter; however, with the vaginal tablet the progesterone concentration decreased over time.

The mean T_{max} was similar for the two formulations (Table 3). However, the time to individual peak plasma concentration, after the gelatin capsule administration, was extremely variable, as evident by a large standard of deviation. This statistically significant difference of variance indicates that the vaginal tablet has a more predictable T_{max} than the gelatin capsule.

A significantly higher C_{max} of 31.53 ± 9.15 nmol/l was achieved by the vaginal tablet, compared to 23.85 ± 9.57 nmol/l achieved by the gelatin capsule. No statistically significant difference was observed between the two formulations in relation to $T_{1/2}$ or to AUC calculated over 24 h. However, the plateau effect of the gelatin capsule resulted in a statistical difficulty in determining the $T_{1/2}$ or AUC values.

The progesterone-containing vaginal tablet was well tolerated by all women in the three studies. The tablets were easily administered, and no patient complained of significant vaginal loss. No subject withdrew from the study because of side effects or adverse reactions to progesterone. No sleepiness, drowsiness, dizziness, or headaches were reported. There was one case of breakthrough bleeding and

several sporadic complaints of mild vulvo-vaginal irritation related to moniliasis. The infection was easily treated by antimycotic agents [20].

5. Discussion

In recent years, it has been established that the vaginal route is preferable for natural progesterone administration. However, the most reliable formulation for patient compliance, as well as therapeutic efficacy, is still under investigation. The different studies conducted by our group have established the pharmacokinetic properties of micronized natural progesterone administered by the novel formulation of a vaginal tablet.

Primarily, we opted to evaluate the pharmacokinetic behavior in postmenopausal non-estrogen primed women to avoid confusion with endogenous progesterone secretion and estrogen influence on vaginal mucosa absorption. The pharmacokinetic results indicated that for assisted reproduction at least 100 mg of progesterone should be administered twice daily. This dosage resulted in a mean C_{max} of 31.61 ± 12.62 nmol/l (Table 1) and in a mean plasma progesterone concentration of 26.08 ± 13.96 nmol/l after continuous use. According to previous studies, serum progesterone concentrations above 3.3 ng/ml (10.5 nmol/l, SI conversion factor 3.18) indicate that ovulation has occurred [22], whereas mid-luteal phase values of 10 ng/ml (31.8 nmol/l) and above demonstrate adequate corpus luteum function [23].

Estrogen can markedly increase vaginal progesterone absorption [24]. Indeed, estrogen priming resulted in higher plasma progesterone concentrations, with a C_{max} of 39.1 ± 13.2 nmol/l (Table 2). Furthermore, the estrogen dose might also influence vaginal absorption. Shushan et al. [25] have shown that a combined vaginal tablet containing 6 mg of ethinyl estradiol and only 50 mg of micronized progesterone resulted in mid-luteal progesterone serum concentrations of 68.6 ± 7.95 nmol/l. We evaluated a lower estradiol dose of 3 mg, since extremely high serum concentrations were obtained even with this lower dose (>7500 pmol/l, unpublished data). Also, the existence of the uterine first-pass effect indicates that lower estrogen and progesterone doses are needed to obtain adequate endometrial and uterine response.

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 and facilitates sustained release. An interesting interaction between the vaginal epithelium and progesterone absorption was observed in relation to age and to estrogen priming. It was shown that women > 40 years old demonstrated enhanced rate of absorption of vaginal progesterone (5.89 ± 3.25 h for the 100 mg dose) compared to younger women (7.25 ± 3.5 h, $P = 0.02$). Delayed absorption was also demonstrated after estrogen priming (Table 2). It is speculated that this observation is related to thinner and atrophic vaginal mucosa in older women.

The comparative pharmacokinetic study further established that the progesterone vaginal tablet is pharmacologically comparable to the progesterone gelatin capsule, which is a commercially available product (Table 3). Moreover, significantly higher C_{max} and more reliable and predictable T_{max} profiles were observed with the vaginal tablet [21]. Continuous daily use of the two preparations was evaluated for patient compliance [21]. Both formulations were well-tolerated with minimal side effects. The vaginal tablet, however, appeared to be more convenient with regard to time schedule and mode of insertion.

In conclusion, natural micronized progesterone given as an effervescent vaginal tablet is a well-tolerated and safe product. As shown in our previous study [20], lack of systemic side effects and lack of influence on liver enzymes and lipid profile indicate a primary effect on the genital tract with direct absorption to the blood stream, bypassing liver first-pass metabolism [26,27]. The endometrial thickness and histologic results demonstrate the efficacy of the progestin vaginal tablet in assisted reproduction. Further evaluation is needed to determine the optimal dose and schedule according to the different infertility indications.

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