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Comparative bioavailability of orally and vaginally administered progesterone*

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Objective: To study the pharmacokinetics of progesterone (P) in healthy premenopausal female volunteers to compare the bioavailability of orally or vaginally administered hormone.

Design: Subjects were randomly allocated to receive either oral P or a vaginal pessary then crossed over to the alternate preparation 1 month later.

Setting: The study was conducted in outpatient setting.

Subjects: All subjects were healthy, normal female volunteers who underwent a physical and gynecological examination before the study. None were using oral contraceptives. Ten subjects (mean age 32.6 ± 7.3 years) entered the study and all completed it.

Interventions: Progesterone was administered as 200 mg of micronized hormone or as a pessary containing 400 mg.

Main Outcome Measure: Plasma levels of P were measured by radioimmunoassay to test the apriori hypothesis of similar bioavailability.

Results: Peak plasma P concentrations attained within 4 hours after oral administration ranged from 8.5 to 70.6 ng/mL, whereas after vaginal administration the peak levels were attained within 8 hours and ranged from 4.4 to 181.1 ng/mL. Considerable interindividual variation was noted. Area under the plasma concentration-time curve for the two formulations was not significantly different ($F = 1.09$; $P > 0.1$; ANOVA).

Conclusions: The two formulations had similar bioavailability. Fertil Steril 1991;56:1034–9

Synthetic progestogens have been widely used for the management of certain gynecological conditions including dysfunctional uterine bleeding, endometrial hyperplasia, premenstrual syndrome, dysmenorrhea, and endometriosis.[1] In combination with estrogens (Es), they have been used as oral contraceptive agents. It has been suggested that synthetic progestogens differ in some respects from those of the naturally occurring hormone and that progesterone (P) is preferable for some therapeutic uses.[2] Furthermore, there are increasing concerns about the side effects of synthetic progestogens. Because of the effects on plasma lipoproteins, the cardioprotective effect of Es may be counteracted,[3] whereas the effects on mood[4] and dermatologic parameters[5] may also limit their usefulness in some patients.

The usual route of administration of natural P is vaginal, rectal, or intramuscular (IM). Progesterone is rapidly absorbed by these three routes of administration with vaginal and rectal administration bioequivalent for equal doses.[2] Intramuscular administration produces higher plasma concentrations that are sustained for longer periods than the other two routes. It has been recommended that daily IM doses be used to produce physiological luteal phase plasma P levels.[2] Where control of plasma P is de-

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sirable, the IM route is preferable because absorption from the vagina is markedly influenced by the formulation used.[6] Oral administration of P, which is more acceptable clinically, has largely been ignored because it was presumed that the hormone is poorly absorbed from the gut, rapidly metabolized, and excreted. Recent studies have suggested that oral forms of P with suitable bioavailability characteristics can be produced, but the extent of absorption (and bioavailability) are markedly influenced by both the vehicle and the particle size.[7]

The present study was undertaken to assess the bioavailability of an oral micronized form of P contained in gelatin capsules compared with that of a vaginally administered form. Comparative bioavailability was assessed by measurement of plasma P concentrations after administration to premenopausal volunteers using a randomized crossover design.

MATERIALS AND METHODS

Subjects

Healthy female volunteers were considered for inclusion in the study if they had no history of renal, hepatic, or gastrointestinal disease, if they had normal findings on physical examination, and if they were within 15% of ideal body weight. Gynecological examination of each volunteer was normal. There was no evidence of vaginal inflammation or infection. Subjects were instructed to refrain from sexual intercourse for 1 day before vaginal administration and 4 days after vaginal administration. Subjects were using adequate contraceptive methods that did not involve the use of hormonal compounds. All subjects gave informed consent for the study that was approved by the Austin Hospital Human Ethics Committee.

Pharmacokinetic Protocol

The study was a crossover design. Random allocation of subjects to either oral (2 × 100 mg tablets) or vaginal (1 × 400 mg suppository) dosing followed by the alternate dosing form was used. At the time of the single dose, each subject was at day 4 to 6 of the menstrual cycle to ensure low endogenous P levels. Only one substance was given in each menstrual cycle, and the study was conducted over two cycles in each subject. Subjects were required to abstain from caffeinated beverages for 24 hours before the day of treatment. On each day of the study, subjects were provided with a standardized breakfast (200 mL of orange juice, 800 kJ of cereal with milk and sugar, 1 piece of toasted bread with a light spread of butter and jam, 250 mL of decaffeinated tea or coffee with milk and 1 teaspoon sugar as desired) before 8 A.M. Subjects reported to the hospital by 8:15 A.M., and P was administered at 8:30 A.M. After vaginal administration, each subject remained in a semireclining position for 4 hours. Blood samples (20 mL) were collected before the dose and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, and 12 hours after the dose from an indwelling heparinized catheter inserted into an arm vein. Additional blood samples were collected at 24, 30, 48, 56, 72, 80, and 96 hours after the dose by venipuncture. This sampling schedule was followed for both formulations. Blood was collected in lithium heparin tubes, centrifuged immediately, and stored frozen at −20°C until analyzed for P.

Pharmacokinetic Analysis

Model independent parameters were estimated from the terminal linear phase of the log plasma P concentration versus time curve. The areas under the plasma concentration time curves (AUC) were measured by the trapezoid rule with extrapolation to infinite time using the last measured concentration divided by the elimination rate constant (β). Terminal phase half-life ($t_{\frac{1}{2}}$) was calculated by linear regression of the unweighted data. The apparent volume of distribution was calculated from the equation $V/f = D/AUC.\ \beta$ where D is the dose. Apparent plasma clearance relative to drug bioavailability (f) was calculated $Cl/f = D/AUC$.

Progesterone Analysis in Plasma

Plasma P concentrations were measured by radioimmunoassay without prior extraction using a commercially available kit (Coat-A-Count; Diagnostic Products Corporation, Los Angeles, CA). This assay has a sensitivity of 0.05 ng/mL, intra-assay coefficient of variation (CV) precision < 10% and interassay CV precision < 10%. Cross-reactivity of the antiserum used with other steroids was low. In particular, the cross-reactivity with P metabolites was <1% and with cortisol and its metabolites was <3%. Samples from each patient for each formulation were run in the one assay to reduce variability. Each sample was run in duplicate, and the variability between duplicates was <10%. Any samples that did

not fall between 20% and 80% binding were repeated, at an appropriate dilution, to fall within this range.

Side Effects

A 15-item scale covering anticholinergic and central nervous system effects was used to record side effects after both administrations. A 4-point scale from 0: absent to 3: severe was used to rate severity. Side effects were rated 1 and 12 hours after the dose, and those occurring at other times and reported spontaneously by the subjects were noted.

Medications

Progesterone was used as an oral formulation (Utrogestan; Laboratories Besins-Iscovesco, Paris, France) of micronized hormone in soft gelatin capsules containing 100 mg of natural P. The alternative formulation was an off-white, waxy suppository (Cyclogest Suppositories; Cox Pharmaceuticals, Barnstaple, United Kingdom) containing 400 mg P in a base of semisynthetic glycerides produced from hydrogenated vegetable oil by interesterification.

Statistics

The comparative bioavailabilities of oral and vaginally administered P were compared using an ANOVA with subjects, treatments, and order of presentation as covariates in the analysis. Other comparisons between treatments were performed using a Mann-Whitney U-test. All statistical procedures were performed using the SPSS-X package[8] and the University of Melbourne VAX computer (Digital Equipment Corporation, Marlborough, MA).

RESULTS

A total of 10 female subjects with a mean ± SD age of 32.6 ± 7.3 years participated in the study. No subjects withdrew from the study because of side effects or adverse reactions to P. Data from the oral administration in one subject are not reported because of loss of samples. After the oral administration of 200 mg of micronized P to nine women, there was a rapid increase of the plasma levels of P (Fig. 1). Individual peak concentrations of 8.5 to 70.6 ng/mL were attained within the 1st 4 hours after administration. Plasma levels declined thereafter to follicular phase levels by 24 to 32 hours.

The administration of 400 mg of P as a vaginal suppository also resulted in a rapid increase in plasma concentrations (Fig. 1). Individual peak concentrations of 4.4 to 181.1 ng/mL were achieved, but the time to peak concentrations varied from 1.5 to 8 hours. The mean plasma P level was maintained at a higher concentration than for oral administration to 24 hours, but thereafter declined to follicular phase levels. There was some evidence of biphasic absorption of P from the mean plasma data curve (Fig. 1), but for most individual data this was not the case. The pharmacokinetic parameters determined for individuals and each dosage form are shown in Table 1.

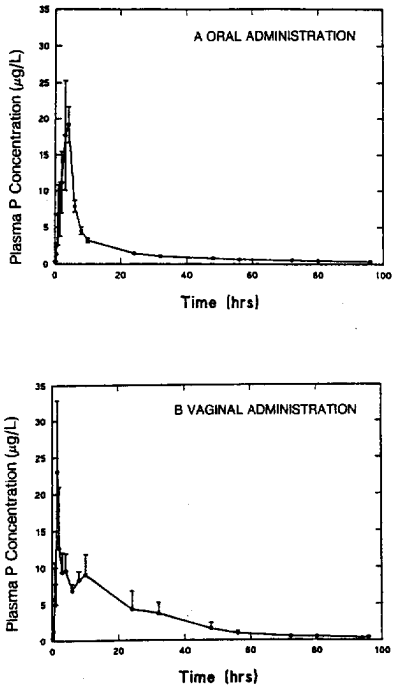

Figure 1 (**A**), Plasma P concentrations (mean ± SEM) after oral and (**B**) vaginal administration to normal volunteers. Subjects received 200 mg orally of micronized P (n = 9) and 400 mg vaginally (n = 10).

An ANOVA was performed on the AUC values using formulation and order of presentation as variables. No significant differences between oral and vaginal forms were observed (overall $F = 1.09$; $P > 0.1$). No significant differences between formulations was observed for c_{max}, the maximum plasma P concentration achieved during dosing (28.0 ± 18.7 ng/mL oral versus 29.2 ± 53.4 ng/mL vaginal; $P > 0.05$, Mann-Whitney U-test). The data for AUC and c_{max} were normalized to 200 mg and compared (Table 2).

Table 1 Demographic and Pharmacokinetic Parameters for Female Volunteers Receiving Two Forms of P

Subject	Age	Weight	Route of administration	β	$t_{\frac{1}{2}}$	AUC	Cl/f	V/f
	y	*kg*		h^{-1}	*h*	$\mu g/h \cdot L^{-1}$	*L/h*	*L/kg*
001	32	73	Oral	0.0220	31.6	151	1,327	827.8
			Vaginal	0.0419	16.6	587	681	223.0
002	40	58.8	Oral	—	—	—	—	—
			Vaginal	0.0216	32.1	196	2,037	1,605.0
003	40	62	Oral	0.0154	44.9	155	1,287	1,345.0
			Vaginal	0.0363	19.1	209	1,912	849.9
004	27	69	Oral	0.0342	20.3	150	1,333	565.5
			Vaginal	0.0272	25.5	369	1,084	577.9
005	23	59.6	Oral	0.0171	40.5	226	885	866.5
			Vaginal	0.0217	31.9	180	2,224	1,716.9
006	34	55	Oral	0.0210	32.9	141	1,414	1,223.7
			Vaginal	0.0190	36.4	197	2,026	1,937.4
007	35	60	Oral	0.0253	27.4	181	1,107	730.3
			Vaginal	0.0132	52.4	96	4,145	5,223.0
008	44	60	Oral	0.0235	29.5	229	871	618.0
			Vaginal	0.0177	39.3	156	2,563	2,419.2
009	28	55	Oral	0.0153	45.2	324	618	732.0
			Vaginal	0.0197	35.1	742	539	496.1
010	23	48	Oral	0.0327	21.2	171	1,169	744.3
			Vaginal	0.0232	29.9	346	1,155	1,036.9
Mean ± SD	32.6 ± 7.3	60.0 ± 7.1	Oral	0.0229 ± 0.0069	32.6 ± 9.3	192 ± 59.1	1,122 ± 268	850.3 ± 264.5
Mean ± SD			Vaginal	0.0242 ± 0.0088	31.8 ± 10.3	308 ± 208	1,837 ± 1,061	1,608.5 ± 1,451.6

Using the normalized data, the bioavailability of the vaginal P was 86.2% of the oral formulation for the same dose. The time to reach maximum concentration was significantly different, with a slower absorption from the vagina than from the gastrointestinal tract (8.1 ± 8.8 hours versus 3.1 ± 1.0 hour; $P < 0.05$, Mann-Whitney U-test). No other statistically significant differences were observed for β, $t_{\frac{1}{2}}$, apparent plasma clearance, and apparent volume of distribution for vaginally and orally administered P.

No subjects were withdrawn from the study because of the side effects of P. Some side effects of mild severity were recorded after both oral and vaginal P and were mostly central nervous system related. More sedation was reported after oral administration. Side effects were maximal at 1 hour for both oral and vaginal preparations. The number of side effects and their relationship to formulation and time after the dose are noted in Table 3.

DISCUSSION

This study has established that 200 mg of P administered orally and 400 mg administered as a vaginal suppository have similar bioavailability. The pharmacokinetics of P showed wide interindividual

Table 2 Pharmacokinetic Parameters for Oral P or Vaginal P

	Oral P[a] (n = 9)	Vaginal P[b] (n = 10)
AUC 0 to 48 ($\mu g/h \cdot L^{-1}$)	149 ± 50.1[c]	257 ± 182[c]
AUC (normalized[d])	149	128.5
C_{max} ($\mu g/L$)	28.0 ± 18.7[c]	29.2 ± 53.4[c]
C_{max} (normalized[d])	28.0	14.6
T_{max} (h)	3.1	8.1

[a] 200 mg.
[b] 400 mg.
[c] Values are means ± SD.
[d] Normalized to 200 mg of P.

Table 3 Side Effects After Two Formulations of P[a]

	Oral		Vaginal	
	1 h	12 h	1 h	12 h
Drowsiness	4	2	1	0
Tired	3	2	1	1
Dizzy	1	1	0	0
Headaches	1	2	1	1
Faint	1	0	1	0
Urinary frequency	1	0	1	0

[a] Values are total number of reports for each effect.

variations. This is in agreement with previous studies of both orally and vaginally administered P. For example, Whitehead et al.[9] found that c_{max} values after 100 mg of oral P administered for 5 days varied from 6.96 to 10.77 ng/mL. After single oral doses of 200 mg of micronized P, Arafat et al.[10] observed c_{max} values of 6.6 to 31.4 ng/mL in seven healthy postmenopausal women. In the present study, c_{max} ranged 8.5 to 70.6 ng/mL in nine healthy premenopausal volunteers. These differences after oral administration may be explained by the presence of different excipients in the formulations used. In support of this explanation, Hargrove et al.[7] noted that after oral administration of micronized P in oil, mean peak plasma concentrations were up to three times greater than micronized, enteric-coated, or plain-milled formulations. Furthermore, food markedly affects the bioavailability of oral formulations of P, much higher availability being observed when taken after a meal, as was the case in the present study.[11] Similarly, certain vaginal tablet formulations were more readily absorbed in dogs than vaginal suppositories.[6] The time to reach maximum plasma concentrations (t_{max}) is also influenced by the nature of the excipients, with micronized P in oil more rapidly absorbed than some other formulations.[7] The mean time to peak was up to 2 hours earlier than in micronized enteric-coated P, for example.

After vaginal administration, the mean time to peak plasma P concentration was 8.15 hours. The mean data, as represented in Figure 1, are weighted by one subject who had a maximum plasma concentration of P of 181.1 ng/mL at 1.5 hours. Despite repeated determinations of P levels in this subject, the results remained the same, within experimental error. We have no explanation for this unexpected finding. Surprisingly, AUC in this subject was not the highest observed and was well within the range of values of the other subjects. A fluctuation of about 20% in plasma P concentration was observed from 3 to 20 hours in these subjects, with evidence for biphasic absorption. This later phenomenon may be because of enterohepatic recycling of P once absorbed from the vagina. Neither Arafat et al.[10] nor Nillius and Johansson[2] observed a similar phenomenon in their studies of vaginally administered P. Both of these groups did observe a broadly similar pattern of plasma concentrations. Peak plasma levels were observed between 3 and 10 hours after the dose with relatively flat plasma concentration-time profiles in the 1st 10 hours. By 24 hours, plasma concentrations had decreased but were generally above follicular phase plasma concentrations.

The absolute bioavailability of P from these preparations was not determined in this study because the hormone was not administered intravenously (IV). The values obtained for clearance and volume of distribution are therefore overestimates and need to be corrected for f, the fraction of the hormone reaching the systemic circulation. In the absence of IV administered hormone, determination of f awaits further study.

A large number of P metabolites have been identified in human plasma.[10] After oral administration, plasma concentrations of the biologically active metabolite 20 α-dihydroprogesterone are present in significant amounts.[9] After oral administration of P, plasma levels of this metabolite and another, 17-hydroxyprogesterone, were lower than the parent compound but followed a similar time course.[9] These metabolites were not measured in the present study, and it is possible that differences in bioavailability of the two formulations may arise because of different rates of appearance and amounts of these metabolites in plasma. We are currently assessing this possibility using specific assays for these metabolites. It has been suggested that specific metabolites of P may mediate the sedative-hypnotic effects of the hormone.[10] Demonstration of differences in metabolite concentrations between those reporting sedative effects and those not reporting such effects would confirm the suggestion. The side effects reported by the volunteers were of mild severity and generally related to sedation. Clinically, this effect might be beneficial, for example, if the P were administered at night or for premenstrual syndrome.[12] For the majority of subjects, side effects were not reported to be of clinical significance.

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