Bioavailability of Progesterone with Different Modes of Administration

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The bioavailability of micronized progesterone (P) was studied by measuring sequential serum P concentrations after a single bolus of 50–200 mg P given sublingually, orally (capsule and tablet), vaginally and rectally (suppositories) during the follicular phase in a group of normally menstruating women. When compared to other modes of P administration, the area under the curve during the first eight hours was twice as high with the rectal route. With 50 and 100 mg P given sublingually and 100 and 200 mg ingested as tablets, peak levels and area under the curve were twice as high with the higher dosage. The response was more sustained with the higher dosage. All subjects exhibited a significant increase in serum P levels over baseline that persisted for at least eight hours. P levels were still increased over baseline at 24 hours in all subjects after the administration of 100-mg vaginal and rectal suppositories and 200-mg tablets. These findings are in general agreement with previous reports showing that luteal phase serum P concentrations can be reached easily with nonparenteral modes of administering micronized P and that oral P administration could become an attractive alternative to the currently used oral mode of administering synthetic progestins.

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Introduction

Progesterone (P) belongs to a group of naturally occurring C-21 steroids. In nonpregnant women its main sites of biosynthesis are the ovaries and the adrenal cortices. In the ovary, P is synthesized by the corpus luteum, with serum concentrations reaching 3–25 ng/mL during the luteal phase of the menstrual cycle, while the concentration remains <1 ng/mL during the follicular phase. Only a small fraction of the circulating P is free; the rest is protein bound. P has a physical half-life of a few minutes. Two-thirds of the P in the blood is metabolized by the liver and is excreted in the urine as pregnanediol and its water-soluble conjugates. Passive diffusion brings P from the bloodstream to its target cells.[2]

P has been used in the management of various gynecologic disorders since it was first synthesized on a commercial scale, in 1934.[27,29] Its clinical usefulness in the past was limited because of its extensive degradation following ingestion. Therefore, orally effective, synthetic progestational agents (progestins) have been substituted in the management of dysfunctional uterine bleeding, endometrial hyperplasia and carcinoma, and endometriosis and have been used in combination with estrogens in oral contraceptives and as cyclic treatment with estrogen during menopause.[27,28]

Progestins fall primarily into two categories: C-19 norsteroid derivatives (i.e., norethindrone and norgestrel) and the 17-hydroxyprogesterone derivatives. All of the progestins have unwanted side effects. Progestins are known to affect lipid metabolism adversely by suppressing high-density-lipoprotein cholesterol.[3,9] Some possess androgenic effects, while others have antiandrogenic and yet others, estrogenic ones.[10] Progestins have not been advocated for use in luteal phase deficiency states because they are known to suppress the ovarian production of P.[11] During pregnancy they are contraindicated because of their possible teratogenic effects.[27]

Most of the problems that can accompany the use of progestins could be avoided or significantly reduced if natural P could be administered in a simple manner that would effect the desired biologic response. Preliminary reports have shown that luteal phase P concentrations in serum and an adequate endometrial response are seen following the oral use of micronized P.[16,20]

This study was designed to evaluate the absorption and bioavailability of micronized P by measuring serum P levels after single-bolus P administration utilizing nonparenteral routes (sublingual, oral, vaginal and rectal) and comparing the mean peak P concentrations, time taken to reach the peak, areas under the curve and duration of P elevation after its administration.

Materials and Methods

In the initial phase of the study, eight healthy, normally menstruating volunteers participated. The contents of one capsule containing 50 mg P were placed under the tongue. The same procedure was repeated 24 hours later, but this time the contents of two capsules (100 mg) were used.

During the second phase of the study, 13 normally menstruating women with premenstrual syndrome (PMS) symptoms participated. They were each given 100 mg P every 24 hours, usually for 4 consecutive days, starting with the sublingual approach and then using an oral capsule and vaginal and rectal suppositories. Some of the participants were studied during two separate cycles.

In the third phase of the study, nine women, several of whom had participated in the second study, were each given 100-mg oral P tablets. Five subsequently were tested with two P tablets (200 mg) 24 hours later or at a later date.

All studies were started at 8 AM during the follicular phase of the menstrual cycle. Studies were initiated as early as the 5th day and completed by the 11th day of the cycle.

The sublingual preparation had 50 mg micronized P (Paddock Laboratories, Minneapolis, MN) and 200 mg lactose in no. 1 gelatin capsules. Each capsule contained 100 mg micronized P. The tablets (Oragest) had 100 mg micronized P in a wax matrix.

The vaginal and rectal suppositories were made up of 100 mg micronized P (Upjohn Laboratories, Kalamazoo, MI) in a cocoa butter base.

A 21-gauge heparin lock needle was inserted intravenously, and blood samples were collected as follows: before P administration and again ½, 1, 2, 4, 6, 8 and 24 hours later. During the second study, an additional specimen was collected at the third and fifth hours; for the third study, an additional collection was made at the tenth hour. Serum was separated by centrifugation and stored in labeled tubes at −20°C until assayed. All samples from the same subject were analyzed in the same assay in duplicate.

Participants were ambulatory throughout the study, and regular meals were permitted. Following administration of the vaginal and rectal suppositories, subjects were kept recumbent for 30–60 minutes.

Direct P measurements on unextracted serum were done with radioimmunoassay (RIA) using kits obtained from Diagnostic Products Corporation, Los Angeles.

Serum estradiol (E_2) was also measured in all the fourth-hour blood samples. Direct E_2 measurements on unextracted serum were done with RIA using kits obtained from Pantex, Santa Monica, CA.

Results

As expected, baseline serum P concentrations were <1 ng/mL. After P administration, all subjects exhibited a significant P increase that persisted for at least eight to ten hours (Tables I–III).

In the first study there was a prompt increase in serum P concentrations after the administration of both 50 and 100 mg sublingual P, with mean peak levels of 10.5 and 17.6 ng/mL, respectively, at one hour (Table I).

In the second study the mean peak P levels after 100 mg sublingual P were 13.5; capsule, 10; vaginal suppository, 8.2; and rectal suppository, 14.0 ng/mL. These peak levels occurred one and two hours after sublingual administration and oral capsules and two to five hours after the vaginal and rectal suppositories (Table II). The area under the curve

Table I *Serum Progesterone Concentrations After Sublingual Administration in Eight Women*

	Progesterone	
Time (h)	50 mg (ng/mL, mean ± SEM)	100 mg (ng/mL, mean ± SEM)
0	0.41±0.11	0.66±0.11
½	8.44±2.16	12.41±2.23
1	10.53±1.75	17.61±3.78
2	6.16±0.95	16.82±2.78
4	2.81±0.56	6.34±1.21
6	1.97±0.17	3.18±0.08
8	1.22±0.18	2.34±0.22
24	0.66±0.11	0.95±0.13

Table II *Serum Progesterone Concentrations After Sublingual, Oral, Vaginal and Rectal Administration*

	Progesterone (100 mg)			
Time (h)	Sublingual (ng/mL, mean ± SEM)	Oral (capsule) (ng/mL, mean ± SEM)	Vaginal (ng/mL, mean ± SEM)	Rectal (ng/mL, mean ± SEM)
0	0.42±0.11	0.96±0.13	0.95±0.23	1.17±0.17
½	6.26±1.37	6.52±3.57	3.47±0.66	6.32±1.62
1	13.47±4.00	5.88±2.12	5.79±0.80	11.21±3.10
2	10.15±2.47	10.03±2.79	7.63±0.70	13.96±4.22
3	5.26±1.05	5.24±1.54	8.21±0.96	12.81±3.40
4	6.47±2.62	3.93±0.74	7.14±0.92	12.21±2.13
5	3.39±0.56	3.19±0.53	7.27±1.31	11.96±2.32
6	2.55±0.28	2.48±0.31	6.06±0.88	11.28±2.23
8	2.42±0.28	2.26±0.17	5.05±0.92	10.09±2.43
10	—	—	5.02±1.65	6.96±2.97
24	0.89±0.21	0.92±0.24	1.83±0.63	2.33±0.64

with rectal P administration was almost double the areas obtained with the other routes (Table IV).

In the third study the mean peak P level after the oral administration of 100 mg P tablets was 3.9 ng/mL and after 200 mg, 10.2. The peak times were four to five hours after administration (Table III).

Mean P levels after the sublingual dose, capsule and 100-mg tablets were administered were back to baseline at 24 hours. However, mean P levels remained elevated at 24 hours after vaginal suppository, rectal suppository and 200-mg-tablet administration, with concentrations of 1.8, 2.3 and 1.2 ng/mL, respectively (Tables I–III). Mean P levels at peak were not significantly different from mean midluteal-phase P concentrations with 50- and 100-mg sublingual administration, 100-mg capsules, 100-mg rectal and vaginal suppositories and 200-mg tablets. When individual data were analyzed in the second study, 2 of 10 subjects using sublingual P, 3 of 10 using oral capsules, 2 of 13 using vaginal suppositories and 2 of 12 using rectal suppositories showed mean peak P levels ⩽5 ng/mL.

The rate of P absorption was quite variable in the same subjects and also between different subjects using the same dose of P and the same or different routes of administration, thus making it impossible to predict the most effective route of absorption. In a few circumstances, when the same dose and route of P were administered in the same subject on more than one occasion, there was good reproducibility.

No side effects, including drowsiness and gastrointestinal complaints, were noted with any of the P preparations. In some of the subjects a portion of the vaginal suppository contents was lost even after recumbency for at least one hour. Five subjects reported minimal vaginal spotting for a few days and/or reported that the subsequent menstrual period occurred earlier than expected. This phenomenon was more evident if P was administered for two or more consecutive days. All had normal resumption of their subsequent menstrual cycles.

Serum E_2 levels remained in the range of 40–200 pg/mL in all subjects. Neither the peak P nor the areas under the curve seemed to correlate with the serum E_2 levels. There was no significant change in serum E_2 in any subject following P administration.

Discussion

Progesterone plays a vital role in human reproductive physiology: it is the only naturally occurring progestational agent. It has had limited usefulness because of its short half-life and extensive degradation following oral administration. Because of these problems, orally effective, synthetic progestins have been substituted.[27]

There are obviously considerable differences between natural P and progestins. Since some progestins have been associated with abnormal fetal development and possess luteolytic properties,[27] there has been increased interest in the clinical and therapeutic need for P.[1] Furthermore, P has been widely advocated for the management of PMS even though this treatment is still controversial and the precise role played by the gonadal steroids in PMS remains poorly understood.[18] Uncontrolled studies have reported favorable results,[5] but most double-blind studies so far have failed to show the efficacy of P over

Table III *Serum Progesterone Concentrations After Oral Administration*

	Progesterone (Oragest)	
Time (h)	100 mg (ng/mL, mean ± SEM)	200 mg (ng/mL, mean ± SEM)
0	0.46±0.15	0.43±0.17
½	0.61±0.15	0.85±0.35
1	1.61±0.56	2.78±1.03
2	2.33±0.54	4.98±1.65
3	3.37±0.48	7.24±1.71
4	3.89±0.43	10.10±2.42
5	3.73±0.49	10.21±3.18
6	3.02±0.49	5.98±1.32
8	2.45±0.44	3.65±0.54
10	1.83±0.25	3.38±0.73
24	0.76±0.21	1.16±0.15

Table IV *Summary of the Progesterone Study*

Variable	Route of administration							
	Sublingual		Sublingual	Oral (capsule)	Vaginal	Rectal	Oral (tablet—Oragest)	
Dose (mg)	50	100	100	100	100	100	100	200
Peak time (h)	1	1–2	1	2	2–5	2–5	4–5	4–5
Peak concentration (ng/mL)	10.5±1.8	17.6±3.8	13.5±4.0	10.0±2.8	8.2±1.0	14.0±4.2	3.9±0.4	10.2±3.2
Range at peak (ng/mL)	(4.5–16.1)	(9.0–33.9)	(3.5–41.5)	(2.0–25.9)	(3.6–14.1)	(1.6–53.1)	(1.8–5.9)	(4.7–18.5)
Area under curve (8 h, cm^2)	61.0	131.0	95.5	76.9	96.0	169.9	43.4	100.0
No. of participants	8	8	10	10	13	12	9	5

placebo.[14,22,23,25] One recent double-blind study showed that an oral formulation of micronized P was effective in alleviating many PMS complaints.[6] The contradictory reports on all therapeutic modalities in PMS are certainly not surprising because of the plethora of subjective symptoms, their variability in intensity from one month to another and the short duration of many studies. Because of the absence of effective and generally acceptable treatments for PMS, the symptomatic improvement that some PMS patients report with P and the absence of significant side effects from P therapy, it is expected that P will continue to be used in PMS for the foreseeable future.

Nillius and Johansson showed that the intramuscular injection of 25 mg of P in oil or 100 mg given by the vaginal or rectal route achieved blood P levels equivalent to those seen during the luteal phase.[17]

Since the intramuscular route of P administration is not therapeutically practical and the vaginal/rectal approach is inconvenient and esthetically displeasing to many women, we studied other nonparenteral approaches to P administration and compared them to the currently utilized vaginal and rectal modalities.

Our results show that serum P levels similar to luteal phase levels can be achieved following a single dose of 100 mg micronized P administered sublingually or orally (in a gelatin capsule) or with vaginal or rectal suppositories. The rapid absorption and disappearance of sublingual P necessitate its use several times per day for it to be therapeutically effective. In one study 50 mg of P suspension was applied sublingually in five postmenopausal women not receiving estrogen replacement.[26] The peak P value was 4 ng/mL at 30 minutes, while in our study, using a similar dose, that value was 10.5 ng/mL at 1 hour. An accurate comparison of serum P levels in different studies is not possible because of variations in assay methods. In a more recent study the bioavailability of P administered as a nasal ointment was assessed.[24]

In our study the capsule showed a slightly delayed peak, but again its disappearance from the circulation was similar to our experience with sublingual P. The sustained P levels after administration of the vaginal and rectal suppositories reflect slow mucosal absorption. The lower P levels from the vagina as compared to the rectum are probably secondary to loss of some of the material from the vagina during the process of absorption. Serum P levels achieved after administration as a vaginal suppository, and presumably as a rectal one, are influenced by the vehicle in which the steroid is given.[14,21] The vehicles used most commonly are cocoa butter and polyethylene glycol. Although 200 mg of P in oral tablets was required to accomplish comparable peak serum P levels obtained with other modes, the P levels after tablets were administered remained elevated for several hours.

Recent interest has been rekindled in and shifted to the search for an orally effective form of natural P. Preliminary studies have shown that micronized P is readily absorbed when given orally and that that route may offer a better alternative to the other modes of P administration and to the use of synthetic progestins.[8,15,16,20,28]

Kincl et al demonstrated that decreasing the particle size with micronization increased dissolution and that coating the P with lipids increased it bioavailability. Kincl et al suggested that the latter approach may enhance lymphatic absorption.[12]

Micronized P combined with oil in a soft gelatin capsule (Utrogestan, Laboratoires Besins Iscovesco, Paris, France) has been evaluated primarily in Europe,[13,16,20,28] and, more recently, the bioavailability of micronized P in oral gelatin capsules was reported on in this country.[15]

Lane et al[13] showed that oral administration of P clearly effects an end organ response within the endometrium, and in a subsequent study Padwick et al[20] concluded that 100 mg oral P in the morning and 200 mg at bedtime increased the serum concentration of P and that the duration of the increase was sufficient to evoke progestational responses in the responsive end organs.

Natural P certainly has advantages over synthetic progestins. Short-term studies have not demonstrated significant changes in serum lipoprotein fractions.[7,19] Exogenously administered P does not suppress endogenous P production but has an additive effect.[1] P therapy initiated in early pregnancy and in association with a corpus luteum defect causes no adverse effect on the pregnancy. P has not been found to be harmful to the developing fetus, and there is some suggestion of its beneficial effects.[27]

Side effects are uncommon with P. Studies on the side effects of long-term P use have not been completed. Dalton followed 40 women who were on P therapy for over ten years and did not note adverse effects. A recent study in women evaluated for infertility suggested that P deficiency increased the risk of premenopausal breast cancer 5.4 times and increased the risk of death from all malignant neoplasms 10.0 times.[4] No adverse drug interactions have been documented. The potential for overdosing is minimal since the P level in pregnancy is 10–30 times higher than the peak level seen during the luteal phase.[2]

Conclusion

Oral treatment with P should have at least metabolic advantages over that with synthetic progestins. Oral P may develop into an attractive option for therapeutic use. Further studies are in progress with the tablet (Oragest) to find the optimum dose, frequency and duration of administration and to maximize target organ effectiveness and delineate the therapeutic benefits.

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References

1. Aksel S, Jones GS: Effect of progesterone and 17-hydroxyprogesterone caproate on normal corpus luteum function. Am J Obstet Gynecol 118:466, 1974
2. Aufrere MB, Benson H: Progesterone: An overview and recent advances. J Pharmaceut Sci 65:783, 1976
3. Bradley DD, Wingerd J, Petitti DB: Serum high density lipoprotein cholesterol in women using oral contraceptives, estrogens and progestins. N Engl J Med 229:17, 1978
4. Cowan LD, Gordis L, Tonascia JA, et al: Breast cancer incidence in women with a history of progesterone deficiency. Am J Epidemiol 114:209, 1981
5. Dalton K: The Premenstrual Syndrome and Progesterone Therapy. London, William Heinemann, 1977
6. Dennerstein L, Spencer-Gardner C, Gotts G, et al: Progesterone and the premenstrual syndrome: A double blind crossover trial. Br Med J 290:1617, 1985
7. Fahraeus L, Larsson-Cohn U, Wallentin L: L-norgestrel and progesterone have different influences on plasma lipoproteins. Eur J Clin Invest 30:447, 1983
8. Ferre F, Uzan M, Janssens Y, et al: Oral administration of micronized natural progesterone in late human pregnancy: Effects on progesterone and estrogen concentrations in the plasma, placenta and myometrium. Am J Obstet Gynecol 148: 26, 1984
9. Hirvonen E, Malkonen M, Manninen V: Effects of different progestogens on lipoproteins during postmenopausal replacement therapy. N Engl J Med 304:560, 1981
10. Huff BB (editor): Physician's Desk Reference. Oradell, NJ, Medical Economics, 1983, p 2067
11. Johansson EDB: Plasma levels of progesterone achieved by different routes of administration. Acta Obstet Gynecol Scand (suppl) 19:17, 1971
12. Kincl FA, Ciaccio LA, Benagiano G: Increasing oral bioavailability of progesterone by formulation. J Ster Biochem 9:83, 1978
13. Lane G, Siddle NC, Ryder TA, et al: Dose-dependent effects of oral progesterone on the oestrogenised postmenopausal endometrium. Br Med J 287:1241, 1983
14. Maddocks S, Hahn P, Moller F, et al: A double-blind placebo-controlled trial of progesterone vaginal suppositories in the treatment of premenstrual syndrome. Am J Obstet Gynecol 154:573, 1986
15. Maxson WS, Hargrove JT: Bioavailability of oral micronized progesterone. Fertil Steril 44:622, 1985
16. Morville R, Dray F, Reynier J, et al: Biodisponibilité de la progesterone naturelle administrée par voie orale: Mésure des concentrations du stéroide dans le plasma, l'endometre et le tissu mammaire. J Gynecol Obstet Biol Reprod (Paris) 11:355, 1982
17. Nillius SJ, Johansson EDB: Plasma levels of progesterone after vaginal, rectal, or intramuscular administration of progesterone. Am J Obstet Gynecol 110:470, 1971
18. Norris RV: Progesterone for premenstrual tension. J Reprod Med 28:509, 1983
19. Ottoson UB, Johansson BG, von Schoultz B: Subfractions of high-density lipoprotein cholesterol during estrogen replacement therapy: Comparison between progestogens and natural progesterone. Am J Obstet Gynecol 151:746, 1985
20. Padwick ML, Endacott J, Matson C, et al: Absorption and

metabolism of oral progesterone when administered twice daily. Fertil Steril 46:402, 1986

21. Price JH, Ismail H, Gorwill RH, et al: Effect of suppository base on progesterone delivery from the vagina. Fertil Steril 39: 490, 1983
22. Sampson GA: Premenstrual syndrome: A double-blind controlled trial of progesterone and placebo. Br J Psychiatr 135: 209, 1979
23. Smith SL, Cleghorn JM, Streiner DL, et al: A study of estrogens and progesterone in premenstrual depression: The family. *In* Proc of Fourth International Congress of Psychosomatic Obstetrics and Gynaecology, Tel Aviv, 1974, p 538
24. Steege JF, Rupp SL, Stout AL, et al: Bioavailability of nasally administered progesterone. Fertil Steril 46:727, 1986
25. Van der Meer YG, Benedek-Jaszmann LJ, Van Loenan AC: Effect of high-dose progesterone on the pre-menstrual syndrome: A double-blind cross-over trial. J Psychosom Obstet Gynecol 2:220, 1983
26. Villanueva B, Casper RF, Yen SS: Intravaginal administration of progesterone: Enhanced absorption after estrogen treatment. Fertil Steril 35:433, 1981
27. Wentz AC: Assessment of estrogen and progestin therapy in gynecology and obstetrics. Clin Obstet Gynecol 20:461, 1977
28. Whitehead MI, Townsend PT, Gill DK, et al: Absorption and metabolism of oral progesterone. Br Med J 280:825, 1980
29. Wintersteiner O, Allen WM: Crystalline progestin. J Biol Chem 107:321, 1934