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INTRAVAGINAL ADMINISTRATION OF PROGESTERONE: ENHANCED ABSORPTION AFTER ESTROGEN TREATMENT*

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A progesterone solution was administered by intravaginal instillation, intramuscular injection, and sublingually to estrogen-deficient women, with or without estradiol (E_2) replacement, and serum progesterone (P) concentrations were measured by radioimmunoassay. Intravaginal application to postmenopausal subjects receiving E_2 gave the highest values of serum P: 10 times baseline at 15 minutes and 30 to 40 times at 1 to 2 hours, with sustained levels for 7 hours and decline to 10 times baseline at 24 hours. Intravaginal application to hypoestrogenic women gave similar results, but of much lower magnitude (highest value, 20 times baseline). Intramuscular injection, in contradistinction, showed gradually increasing levels over the study period, up to 30 times basal values at 24 hours. In contrast, sublingual application produced very modest serum increases, to approximately 10 times baseline within 2 hours and return to basal value at 24 hours.

Since the most rapid and highest levels were observed by vaginal application to postmenopausal women receiving estrogen, and considering that the vagina has been similarly shown to be very effective for estrogen absorption, it is conceived that full hormone replacement could be accomplished in the deficient states by cyclic vaginal application of both steroids. Fertil Steril 35:433, 1981

It is now accepted that cyclic administration of progesterone to women receiving long-term estrogen replacement may be protective against the development of endometrial hyperplasia and neoplasia. This is based upon the knowledge that progesterone exerts antagonistic effects upon estrogen responses by decreasing the tissue content of estrogen receptors.[1] Progesterone interferes with the replenishment of estrogen receptors, thereby inhibiting the estrogen-induced growth of its target organs.[2]

Since the vaginal route has been shown to be most efficient for the absorption of estrogen,[3] the present study was undertaken to evaluate the vaginal and sublingual routes as alternative ways to deliver progesterone to postmenopausal women. If both steroids could be administered by a single route, that would appear to afford desirable simplicity and convenience.

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MATERIALS AND METHODS

Intravaginal Application of Progesterone. Two groups of estrogen-deficient women volunteered for these studies. Four women were receiving Premarin (Ayerst Laboratories, N. Y.), 1.25 mg/day, at the time of the investigations; five women had not received any hormone for at least 6 weeks.

A commercially available progesterone suspension, 50 mg/ml, containing per milliliter: sodium carboxymethyl cellulose, 2 mg; methylcellulose, 0.3 mg; dioctyl sodium sulfosuccinate, 0.15 mg; and thimerosal, 0.08 mg, as preservative in water for injection with sodium phosphate buffers, was used for administration. A portion of the suspension (1 ml) was deposited in the posterior vaginal vault with a vaginal speculum. Subjects remained in the recumbent position for 1 hour after progesterone application and were allowed to ambulate thereafter. Diet was not restricted. Blood samples were obtained through an indwelling catheter inserted in an arm vein and kept open with slow infusion of saline. Two basal samples of blood were obtained at 15-minute intervals. After the intravaginal progesterone instillation, blood samples were obtained at 5, 15, 30, and 60 minutes, and every hour thereafter until 7 hours after application. Subjects were then instructed to return to the hospital the following day and a 24-hour sample was obtained.

Intramuscular Injection of Progesterone. A group of eight postmenopausal women volunteered to receive progesterone intramuscularly. Three subjects had not received any hormone for more than 6 weeks, and five women were currently taking Premarin, 1.25 mg/day, as estrogen replacement. The sampling schedule and procedure were the same as those for the intravaginal groups. The subjects received 1 ml of the progesterone preparation described above, intramuscularly, at time zero. There was no significant difference in the pattern or magnitude of absorption between the women receiving estrogens and the hypoestrogenic group. Consequently, they were combined for the analysis.

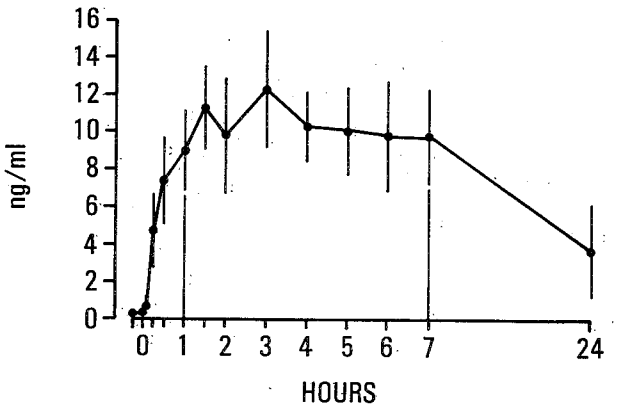

FIG. 1. Serum progesterone concentrations (means ± standard error) following intravaginal application of 50 mg of progesterone suspension to four postmenopausal women receiving estrogen replacement.

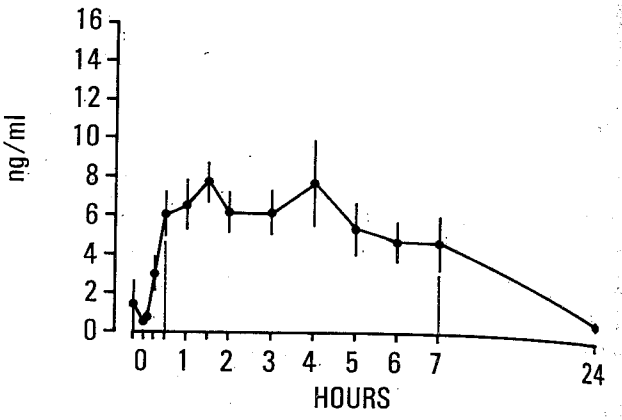

FIG. 2. Serum progesterone concentrations (means ± standard error) following intravaginal application of 50 mg of progesterone suspension to five postmenopausal women not receiving estrogen replacement.

Sublingual Administration of Progesterone. Five postmenopausal women received 1 ml of the same progesterone preparation via sublingual instillation. None had received any hormone within the previous 6 weeks. The sampling and the procedure were identical with those described for the other groups.

Serum concentrations of progesterone were measured by radioimmunoassay.[4]

RESULTS

The absorption of progesterone through the vaginal mucosa was very rapid, as demonstrated by the serum progesterone levels attained (Fig. 1). The immediate appearance of the hormone in peripheral circulation resulted in more than a 10-fold increment above baseline values in the samples obtained only 15 minutes after administration. The values then reached maximal levels within 1 or 2 hours, between 30 and 40 times (12.25 ± 3.11 ng/ml) the basal value (0.34 ± 0.05 ng/ml), remaining at that high level during the 7 hours of frequent sampling and then declining at 24 hours to approximately 10-fold pretreatment levels (3.68 ± 2.42 ng/ml). While these findings were observed in the group of postmenopausal women receiving estrogen replacement, the administration of vaginal progesterone to the group of postmenopausal women not receiving estrogen (Fig. 2) resulted in a similar pattern of serum levels, but maximal values reached a concentration only 20 times (6.55 ± 1.28 ng/ml) greater than the baseline and there was a gradual decline thereafter that approached the basal value within 24 hours (0.98 ± 0.24 ng/ml).

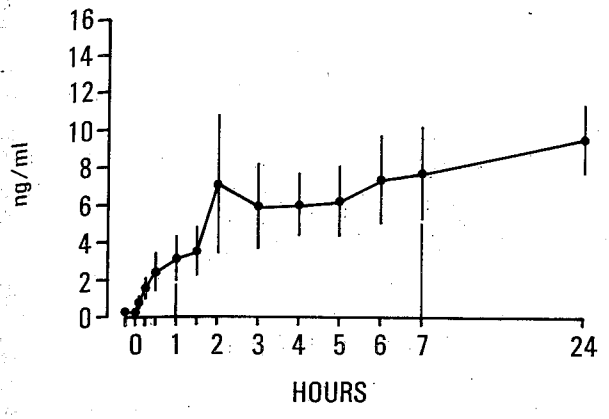

FIG. 3. Serum progesterone concentrations (means ± standard error) following intramuscular injection of 50 mg of progesterone suspension to five postmenopausal women receiving estrogen replacement and three postmenopausal women not receiving estrogens.

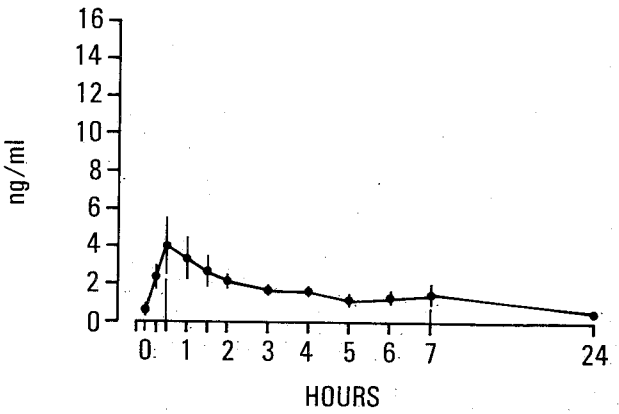

FIG. 4. Serum progesterone concentrations (means ± standard error) following sublingual application of 50 mg of progesterone suspension to five postmenopausal women not receiving estrogen replacement.

Intramuscular injection (Fig. 3) of the same progesterone solution resulted in a somewhat slower appearance of the hormone in the serum with levels gradually increasing over the 7 hours of frequent sampling to a value approximately 20-fold greater than baseline (7.74 ± 1.52 ng/ml); however, rather than a decline, a persistently elevated level, 30 times greater than baseline, was noted at 24 hours (8.84 ± 1.93 ng/ml).

Although sublingual administration (Fig. 4) resulted as well in the rapid appearance of progesterone in serum, the values were much more modest. Nevertheless, some of the serum levels in the first 2 hours reached 10 times baseline values (3.97 ± 1.50 ng/ml); 24-hour levels had returned to baseline.

All values for all groups are shown in Table 1.

When all of the groups were compared among themselves, the following observations were made (Table 2). When total progesterone absorbed was calculated as the area under the curve, it was apparent that subjects receiving vaginal progesterone after estrogen treatment absorbed as much as the group receiving it intramuscularly, whereas the group receiving vaginal progesterone without estrogen pretreatment absorbed only half as much. The initial rate of absorption was calculated as the net increase at 1 hour and showed that the groups receiving progesterone vaginally had an increase 2 to 3 times that of the groups receiving progesterone intramuscularly or sublingually. Although vaginal application resulted in a faster initial absorption, intramuscular administration resulted in a much

TABLE 1. *Serum Progesterone Concentrations by Radioimmunoassay[a] following Administration of Progesterone by Different Routes to Postmenopausal Women*

Sample	Time	Vaginal		Intramuscular	Sublingual
		E_2 treatment	No E_2 treatment		
		ng/ml	*ng/ml*	*ng/ml*	*ng/ml*
1	Baseline	0.36	1.45	0.28	
2	Baseline	0.34	0.55	0.24	0.63
3	5 min	0.71	0.80	0.76	
4	15 min	4.71	3.01	1.52	2.35
5	30 min	7.38	6.05	2.39	3.97
6	60 min	8.99	6.55	3.08	3.30
7	90 min	11.27	7.74	3.44	2.64
8	120 min	9.80	6.19	7.00	2.14
9	3 hr	12.25	6.17	5.83	1.69
10	4 hr	10.25	7.68	5.91	1.63
11	5 hr	10.03	5.34	6.13	1.16
12	6 hr	9.76	4.70	7.29	1.30
13	7 hr	9.74	4.69	7.63	1.47
14	24 hr	3.68	0.98	9.52	0.50

[a]Sensitivity 0.01 ng.

TABLE 2. *Comparison of Amount and Rate of Progesterone Absorption in Estrogen-Treated and Nontreated Groups and Among Groups Receiving Progesterone via Different Routes*

	Vaginal		Intramuscular	Sublingual	p[a]
	E_2 treatment	No E_2 treatment			
Total absorbed (ng/ml/24 hr)[b]	206 ± 45	87 ± 21	184 ± 42	26 ± 7	<0.05
Net increase at 1 hr (ng/ml)	8.9 ± 2.1	6.6 ± 1.3	3.0 ± 1.2	2.9 ± 1.1	<0.05
Net change during last 17 hr (ng/ml)	−7.0 ± 2.5	−3.6 ± 1.1	1.9 ± 1.8	−1.1 ± 0.5	<0.01
Time to peak (hr)	2.9 ± 0.5	3.0 ± 0.7	14.4 ± 3.6	1.3 ± 0.5	<0.01

[a]All p values calculated by analysis of variance.
[b]Area under the curve.

longer absorption; during the last 17 hours, progesterone levels in the group receiving intramuscular injections continued to rise while in all other groups the levels fell. The time to peak values, a function of both rate and amount of absorption, was by far longest in the group receiving intramuscular injections.

DISCUSSION

The observation of such a rapid increase in serum progesterone levels following vaginal application of progesterone defines the vaginal mucosa as a very effective site for absorption and delivery of the hormone to the circulation. The notion that the vaginal route may be appropriate for steroid administration has been previously explored with regard to both estrogen and progesterone.[3, 5, 6] Rigg et al.[3] from this laboratory showed that intravaginal application of micronized 17β-estradiol (E_2) resulted in rapid and sustained absorption of the hormone with circulating E_2 levels greater than 100 times basal levels at 2 hours and greater than 6 times basal levels even at 24 hours. Nillius and Johansson[5] and Johansson[6] compared vaginal, rectal, and intramuscular routes for progesterone administration in cycling women in the preovulatory phase and in postmenopausal women receiving estrogen replacement. Vaginal insertion of 100 mg of progesterone in cocoa fat, in suppository form, to six cycling women resulted in peak levels of progesterone (mean 13.5 ng/ml) within the first 4 hours, with a gradual decrease during the next 8 hours, and values higher than baseline in some women at 24 hours and even 36 hours. The very rapid increase in serum progesterone levels in our studies as compared with these data, for similar vaginal progesterone applications, suggests that the vehicle used for the suspension of the hormone may influence the absorption rate from the same vaginal site. Our studies utilized an aqueous suspension of progesterone, whereas Nillius and Johansson[5] instead used progesterone suppositories with the hormone dissolved in cocoa fat. Although the sampling schedules were different, it is likely that liquid suspension of the hormone results in greater contact surface for absorption, hence the almost immediate detection of serum level increments shown here. An interesting additional element in our studies was the observation that, after vaginal application of progesterone to postmenopausal women receiving estrogen replacement, the measured serum concentrations of progesterone reached much higher levels than those of postmenopausal women not receiving estrogen replacement. It is conceivable that anatomical and metabolic differences in the estrogen-treated group were responsible for the apparent differences. Vaginal tissue vascularity and higher levels of serum carrier proteins could be the mechanisms behind the much greater absorption documented.[7]

Since the best results in vaginal absorption of the hormone occurred in those subjects previously exposed to estrogens, it follows that postmenopausal women receiving estrogen replacement would derive the most benefit from this modality of progesterone administration. Furthermore, since the vaginal route was likewise shown to be very effective and predictable for estrogen absorption following vaginal E_2 application, as mentioned above,[3] it is possible to envision both steroids being administered cyclically by the same vaginal route as an acceptable alternative for full replacement in the deficient states.

Although the vaginal route appears to be a fast and efficient way to deliver progesterone to the circulation, it is clear that hormone application to the vagina is far less convenient than oral ingestion. However, a real advantage is the possibility of using natural progesterone rather than the orally active synthetic progestins. Parenteral administration, of course, permits the use of

natural hormone, but vaginal application appears potentially more convenient than injections, especially for long-term treatment. Pharmacologic perfection of a suitable vehicle should necessarily follow to facilitate vaginal application of progesterone as a viable and appealing alternative in the clinical setting.

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