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Influence of the Maturity of the Vaginal Epithelium upon the Absorption of Vaginally Administered Estradiol-17β and Progesterone in Postmenopausal Women

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Abstract. Serum concentrations of estradiol-17β and its metabolites estrone (unconjugated) and total estrone (mainly estrone sulfate) and of progesterone were measured before and after application of one vaginal suppository containing 250 μg estradiol-17β and 10 mg progesterone to 10 previously unsubstituted healthy postmenopausal women with normal pretreatment serum steroid levels. Vaginal hormone cytology was performed prior to administration of the estrogen-progesterone combination. An atrophic vaginal mucosa was found in 5 and a moderate proliferation in the other 5 women. A significant association was found between proliferation and pretreatment values of estrone, but not with other steroids. There was a clear, significant association between steroid absorption kinetics and the condition of the vaginal mucosa as indicated by cytological data: significantly higher absorption was found in women with an atrophic vaginal mucosa.

Introduction

The efficacy of vaginal absorption of steroids and related compounds is well established [for reviews see refs. 1 and 2]. Most studies indicate a more efficient absorption in unsubstituted postmenopausal women than in those receiving estrogen replacement therapy or in premenopausal women [for a review see ref. 2]. However, even unsubstituted healthy women, being more than 3 years postmenopausal and with normal, i.e., low, peripheral estrogen levels, show a great variability in vaginal steroid absorption [2]. Although estrogen deficiency usually transforms the postmenopausal vaginal mucosa into an atrophic condition, a proliferated vaginal epithelium can sometimes be observed several years after the menopause, even in patients with low estrogen levels [3, 4]. As far as we know from the literature, no studies on the relation between vaginal steroid absorption and vaginal cytology in unsubstituted postmenopausal women have been reported. We have, therefore, investigated the absorption kinetics of an estrogen-progesterone combination in healthy unsubstituted postmenopausal women with different degrees of maturity of the vaginal epithelium.

Materials and Methods

Subjects and Pharmaceutical Preparation

The clinical material comprised 10 postmenopausal women (age 52–67 years; mean 60.3 years) 3–16 years after menopause (mean 9.7 years). All women had undergone a natural menopause and had a previous history of regular menstruations. They were all apparently healthy and had no clinical or laboratory signs of hepatic, biliary, intestinal, or renal malfunction or any endocrine abnormalities. Except for the estrogen-progesterone combination described below, they were all free of medication and had never received any previous postmenopausal estrogen replacement.

One vaginal suppository containing 250 µg micronized estradiol-17β (E_2) and 10 mg of micronized progesterone (Klimavag®; Novo Industri, Bagsvaerd, Denmark) was applied deep intravaginally at 08.00 h. Venous blood samples were taken before and 2, 4, 6, 8, 10, 12, and 15 h after application. Serum was separated by centrifugation and stored at −20 °C until analyzed.

The study was approved by the Ethical Committee, Huddinge University Hospital, and informed consent was obtained from all women participating in the study.

Hormone Analysis

Serum concentrations of E_2 and progesterone were determined radioimmunologically in untreated serum using commercial kits from Diagnostic Products (Los Angeles, Calif., USA). Unconjugated (E_1) and total estrone (tE_1; mainly estrone sulfate) in serum were determined by radioimmunoassay after ether extraction as described previously [5]. In the tE_1 assay enzymatic hydrolysis of estrone conjugates preceded the extraction. Detection limits and within and between assay coefficients of variation were for E_2 35 p*M* and 5 and 9%, for progesterone 0.15 n*M* and 5.8 and 7.2%, for E_1 30 p*M* and 7 and 9.8%, and for tE_1 0.3 n*M* and 7 and 8.9%.

Vaginal Cytology

Vaginal smears were taken from all women prior to administration of the vaginal suppository containing the estrogen-progesterone combination. The samples were stained according to the method of Papanicolaou and examined by a cytologist (A.H.). The hormonal status was evaluated by using the pycnotic index as well as the maturation index [6].

Statistical Methods

Spearman's rank correlation test, the Mann-Whitney U test, and the t test for unpaired observations were used according to the distribution of the individual values.

The absorption of a steroid during 6 and 15 h after administration was expressed as the area under the curve increment (AUC). For each interval between adjacent samples, an area was calculated as the product of (the mean concentration during the interval − the concentration at 0 h) and the time of the interval. AUC is the sum of the areas during the sampling intervals covered by the observation period (AUC_{0-6} = 0–6 h and AUC_{0-15} = 0–15 h).

Results

Data on age, time after menopause, serum steroids, and vaginal cytology before application of estrogen-progesterone vagitories are given in table 1. An atrophic mucosa was found in 5 and a moderate proliferation in the other 5 women. There were no significant differences between the two groups of women with respect to age, time after menopause, and serum steroid levels except for a significantly higher mean serum level of E_1 in the women with a moderately proliferated mucosa. Geometric mean steroid concentrations and individual concen-

Table 1. Age, time after menopause, serum steroids, and vaginal cytology in postmenopausal women before application of estrogen-progesterone vaginal suppositories

Patient No.	Age years	Time after menopause years	Serum steroid level				Pycnotic index, %	Maturation index		
			E_2 p*M*	E_1 p*M*	tE_1 n*M*	progesterone, n*M*		surface cells, %	intermediate cells, %	parabasal cells, %
Atrophy										
2	60	9	<35	107	0.39	0.3	0	0	4	96
5	57	6	<35	66	0.44	0.5	0	0	0	100
6	67	17	<35	118	0.33	0.4	0	0	0	100
9	66	16	<35	49	1.27	0.9	0	0	0	100
10	59	9	<35	179	0.59	0.3	0	0	0	100
Mean	61.8	11.4	<35	104	0.61	0.5	–	–	–	–
SEM	2.0	2.2	–	23	0.16	0.1	–	–	–	–
No atrophy										
1	53	4	<35	184	0.61	0.5	1	1	98	1
3	67	9	<35	203	1.67	0.5	1	1	86	13
4	52	3	<35	157	0.52	0.4	2	2	98	0
7	58	16	<35	175	0.51	0.8	1	1	95	4
8	64	8	<35	125	0.95	0.7	3	3	97	0
Mean	58.8	8.0	<35	167	0.85	0.6	–	–	–	–
SEM	2.9	2.3	–	13	0.22	0.1	–	–	–	–
Significance of difference between mean values (t- test)	NS	NS	NS	p<0.001	NS	NS	–	–	–	–

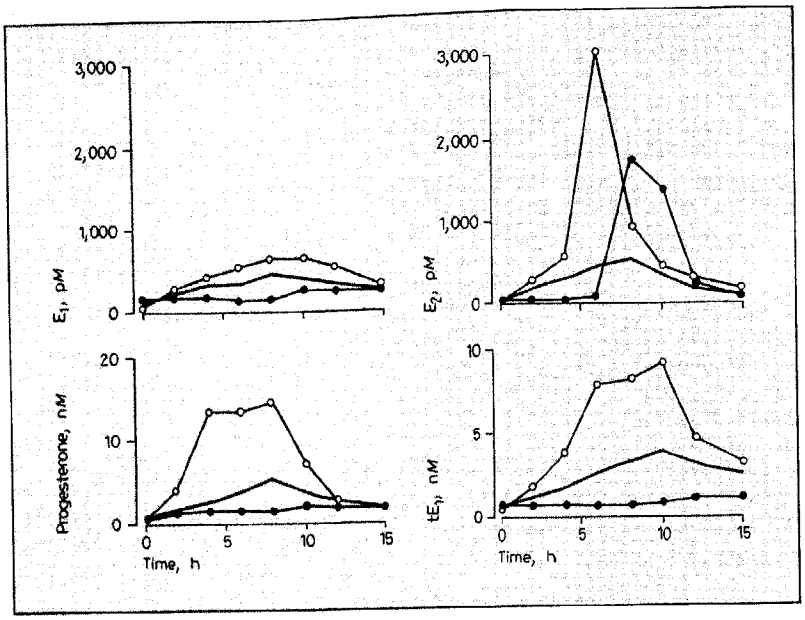

Fig. 1. Peripheral serum concentrations of E_2, E_1, tE_1, and progesterone before and after application of one vaginal suppository containing 250 µg E_2 and 10 mg progesterone to 10 healthy, previously unsubstituted postmenopausal women. Geometric mean (——) and individual values for the subjects having the lowest (●) and highest (○) AUC_{0-6}. For explanations, see text.

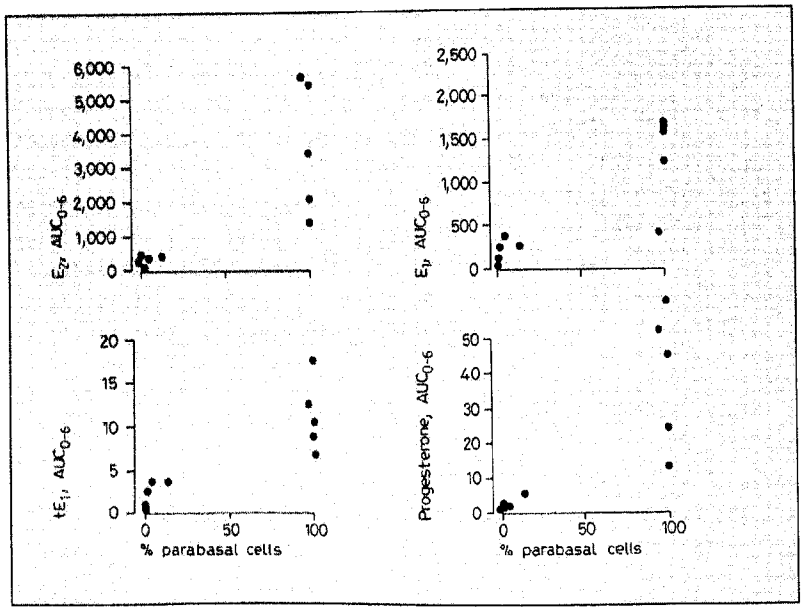

Fig. 2. Relation between vaginal steroid absorption, expressed as AUC_{0-6}, and percent parabasal cells before treatment in 10 healthy, previously unsubstituted postmenopausal women given one vaginal suppository containing 250 µg E_2 and 10 mg progesterone. For explanations, see text. AUC values, see table 2.

trations in the women showing the highest and the lowest AUC_{0-6} are given in figure 1. The results again indicate a considerable variation in vaginal steroid absorption even in unsubstituted postmenopausal women.

Geometric mean and range for AUC values in women with atrophic and with moderately proliferated mucosa are given in table 2. Significantly higher mean AUC values were found in women with atrophic mucosa for all steroids, except AUC_{0-15} for E_2. Identical results were obtained when the women were grouped according to maturity index surface cells (data not shown).

The relation between AUC_{0-6} and the percentage of maturity index parabasal cells is illustrated in figure 2. Significant positive correlations (Spearman's rank correlation test) were obtained between AUC and parabasal cells for all four steroids studied. For AUC_{0-15} and parabasal cells, the following correlations were obtained: E_2: $r_s = 0.22$ (NS); E_1: $r_s = 0.85$ ($p < 0.01$); tE_1: $r_s = 0.85$ ($p <$

Table 2. Geometric mean and range for AUC values for E_2 and E_1 (p$M \times$ h) and tE_1 and progesterone (n$M \times$ h) in postmenopausal women with atrophic and with moderately proliferated vaginal mucosa

		Atrophic vaginal mucosa		Moderately proliferated vaginal mucosa		Significance of difference between mean values (Mann-Whitney U test)
		mean	range	mean	range	
E_2	AUC_{0-6}	3,134	1,362–5,688	251	60–468	$p < 0.05$
	AUC_{0-15}	10,938	9,180–13,515	3,180	690–17,925	NS
E_1	AUC_{0-6}	1,153	402–1,644	122	12–257	$p < 0.05$
	AUC_{0-15}	4,100	2,505–5,535	71	0–3,105	$p < 0.05$
tE_1	AUC_{0-6}	10.71	6.66–17.40	1.71	0.48–3.54	$p < 0.05$
	AUC_{0-15}	53.12	35.10–78.45	8.54	1.50–34.80	$p < 0.05$
Progesterone	AUC_{0-6}	33.0	12.6–57.6	2.0	1.2–5.4	$p < 0.05$
	AUC_{0-15}	110.0	81.0–138.0	10.2	3.0–82.5	$p < 0.05$

NS = Not significant.

0.01), and progesterone: $r_s = 0.69$ ($p < 0.05$). Very similar, but negative correlation coefficients, at the same significance levels, were found when AUC values were related to maturity index intermediate cells (data not shown).

Discussion

The serum steroid levels before application of the estrogen-progesterone vaginal suppository were well below the upper reference limits in all subjects. Nevertheless, a certain degree of estrogen stimulation of the vaginal mucosa was found in half of the women. Significantly higher E_1 levels in these women were the only difference found with respect to serum hormones. A similar association between vaginal hormone cytology and serum 'total' estrogens, i.e., $E_1 + E_2$, in postmenopausal women has previously been shown by Benjamin and Deutsch [3]. These findings further confirm the superiority of E_1 or $E_1 + E_2$ assay compared to E_2 when studying the estrogen status in subjects with mainly extragonadal estrogen sources, i.e., postmenopausal women and men [7, 8].

There was a clear, significant association between steroid absorption kinetics and the condition of the vaginal mucosa, as indicated by cytological data. Thus, our results further confirm the impact of estrogen stimulation on vaginal steroid absorption kinetics, even within unsubstituted postmenopausal women with normally low peripheral estrogen levels.

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