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ESTRIOL: ABSORPTION AFTER LONG-TERM VAGINAL TREATMENT AND GASTROINTESTINAL ABSORPTION AS INFLUENCED BY A MEAL

Gun Heimer and Doris Englund

From the Department of Obstetrics and Gynecology, University Hospital, Uppsala, Sweden

Abstract. This study was designed to evaluate the vaginal absorption of estriol when given as a 21-day treatment. Vaginal absorption was compared with the oral absorption of a known estriol preparation (Triovex^R, Leo AB, Sweden). One mg of estriol was administered intravaginally once a day for 21 days to 6 menopausal women. Plasma concentrations of unconjugated estriol were measured by a specific RIA-method at frequent intervals during 24 hours on the first and 21st day of treatment. One month later, 10 mg of estriol was given once orally and plasma estriol concentrations were measured in the same way. At vaginal administration, the absorption of estriol was very effective. When measured on the 21st day, the absorption had declined significantly but was still nearly in the same range as after oral administration of 10 mg of estriol. At oral administration, there was an initial plasma estriol elevation for 3 hours only followed by a second one immediately postprandially. It is concluded that estriol is readily absorbed from the vagina, but the absorption does decline significantly during prolonged treatment. A large single oral dose of estriol provides initially a high plasma estriol concentration but also a second one induced by eating a meal, possibly indicating an enterohepatic recirculation of estriol.

Key words: Estriol, vaginally, orally, menopausal

Estrogen therapy for estrogen-deficient women is well established, but the management of this treatment is still not solved. The choice of estrogen, the dosage, as well as the route of administration are still matters for research.

The alleged relationship between estrogens and endometrial cancer has stimulated a re-evaluation of estriol. The usual claim that estriol is a weak estrogen which affects the vagina and cervix uteri only and not the endometrium has been contradicted in recent studies (3, 8). As pointed out in these studies and in earlier animal experiments (1), estriol is a short-acting estrogen, which exerts estrogenic stimulation when the plasma estriol elevation is prolonged. The current oral singledose regimen using low dosages provides elevated plasma estriol levels for only a few hours and hence probably does not stimulate the endometrium.

The aim of this study was to test the efficacy of vaginal absorption of 1 mg estriol as judged by plasma estriol levels and the duration of the estriol elevation so induced. Also, the estriol absorption after long-term vaginal administration was studied, as the maturation of the vaginal epithelium has been claimed to affect the estrogen absorption (5).

The vaginal absorption of 1 mg estriol was compared with the gastrointestinal absorption of 10 mg estriol given orally as a single dose.

MATERIAL AND METHODS

Six healthy menopausal women, 53 to 62 years of age, gave their informed consent to participate in the study. None had had any vaginal bleeding for at least 2 years or had recieved estrogen therapy during the last 6 months.

One mg estriol (ovula containing estriol supplied by Leo AB, Sweden) was inserted into the vagina every morning for 21 days. Peripheral venous plasma samples were collected at frequent intervals for 24 hours on the first and 21st day of treatment. Plasma concentrations of unconjugated estriol were measured by a specific radioimmunoassay (RIA) (2).

Before the oral administration of 10 mg estriol (Triovex^R, Leo AB), one month without treatment was required to have elapsed. The women were instructed not to eat or to drink 8 hours before and until 4 hours after drug administration, when a meal was allowed. Plasma concentrations of estriol were measured in the same way when estriol was given orally as when administered intravaginally. Plasma concentration curves ($AUC_{0\text{-}24\text{-}hours}$) were calculated. For statistical analysis, Wilcoxon's non-parametric test was used. The area below the observed plasma concentration time curve was calculated using the trapezoid rule and the Wilcoxon signed rank sum test for percentual change.

RESULTS

The plasma estriol elevations measured after vaginal administration of 1 mg estriol on day one and on day 21 of treatment and after oral administration of 10 mg estriol are presented in Fig. 1, 2 and 3.

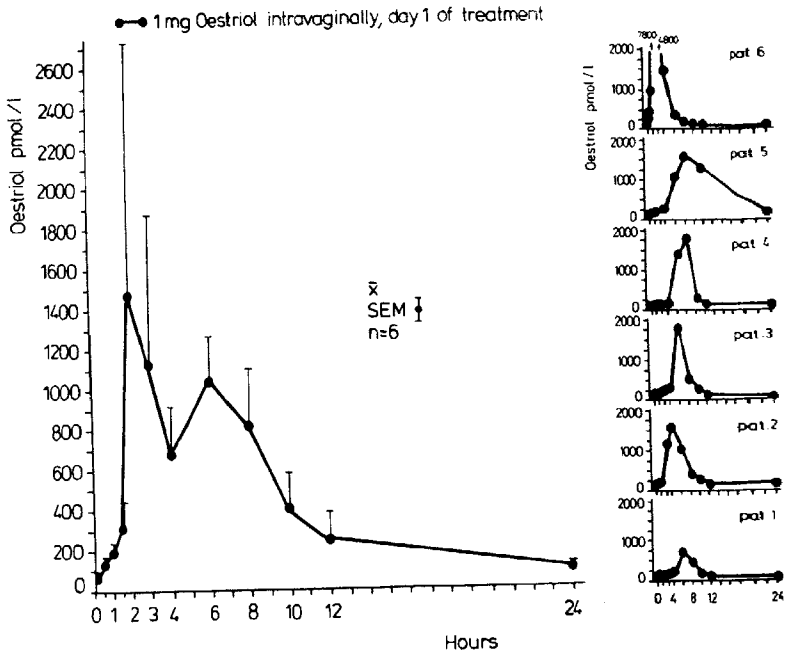

Fig. 1. Plasma levels of estriol after intravaginal administration of 1 mg estriol, day 1 of treatment. The results in each individual are shown on the right. The mean of 6 subjects and standard error of the mean are shown on the left.

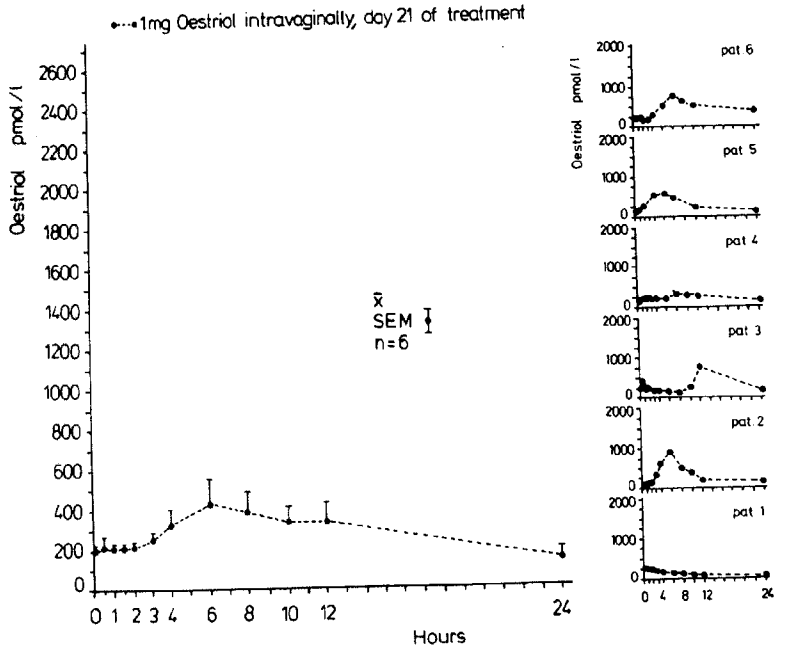

Fig. 2. Plasma levels of estriol after intravaginal administration of 1 mg estriol, day 21 of treatment. The results in each individual are shown on the right. The mean of 6 subjects (±S.E.) are shown on the left.

The subjects are referred to as numbers one to six. From the figures, it is evident that the interindividual estriol absorption, as reflected by plasma estriol elevation, is considerable both after vaginal (Figs. 1, 2) and oral (Fig. 3) administration. However, the tendency in the plasma estriol pattern is the same.

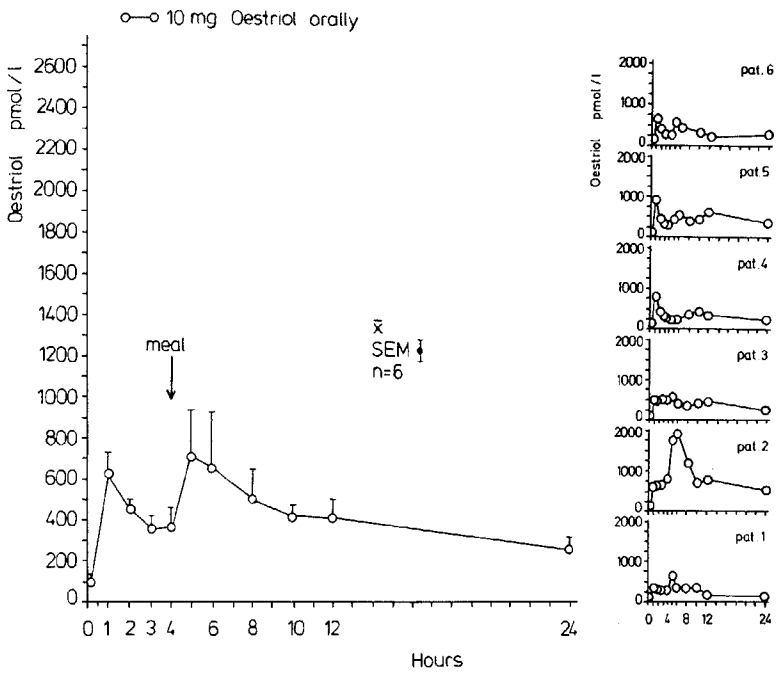

Fig. 3. Plasma levels of estriol after oral administration of 10 mg estriol. The results in each individual are shown on the right. Mean of 6 subjects (±S.E.) are shown on the left.

One mg estriol administered intravaginally on day one of treatment (Fig. 1) was absorbed slowly during the first hours. Then a rapid and marked increase in plasma estriol levels lasting for about 6 hours was seen. In one subject (Fig. 1, right, patient 5), the plasma estriol elevation seems to be very prolonged. This probably does not reflect the real pattern, as blood samples were not collected between the 12- and the 24-hours samples.

When the plasma levels of estriol were measured on the 21st day of treatment (Fig. 2), there was a different plasma estriol pattern compared with that seen on day one of treatment. The estriol absorption had declined, as reflected by the lower plasma estriol concentrations and the plasma estriol level was more constant than during the first treatment day, when the diurnal variation was considerable. In 2 subjects (Fig. 1, right, patients 1 and 4), the plasma estriol elevation was only minor.

When the area below the curve ($AUC_{0\text{-}24\text{-hours}}$) was calculated (Table I), the plasma estriol elevation differed significantly between day one and day 21 of vaginal estriol treatment. The vaginal absorption of estriol on day 21 was slightly more than 30% lower ($p = 0.05$) than the vaginal absorption of estriol recorded after the first day of treatment. The estriol level before vaginal insertion of estriol ovula on day one and day 21 was also different ($p < 0.05$), indicating a certain accumulation of estriol (Table II $C_{0\text{-hours}}$). The estriol concentrations at 24 hours after the 1st and 21st day of treatment, however, were in the same range (Table II $C_{24\text{-hours}}$). Hence, the $AUC_{0\text{-}24\text{-h}}$, $C_{0\text{-h}}$ and $C_{24\text{-h}}$ values indicate that the amount of available estriol in the peripheral circulation is greater after the first than after the last dose.

When a single oral 10 mg dose of estriol was given (Fig. 3), an initial plasma estriol elevation was seen in all subjects. This first elevation lasted for about 3–4 hours in patients 4 and 6 and was then followed by a second elevation lasting for at least another 6 hours.

Table I. *Comparison of $AUC_{0\text{-}24\ h}$ obtained after intravaginal administration of estriol.*

Patient	Day 1	Day 21	Percentage decrease
1	4000	2219	44.5
2	8906	7031	21.1
3	7697	8460	−9.9
4	8972	5580	37.8
5	18634	6655	64.3
6	16091	10514	34.7
Mean	9133	6743	32.1 ($p = 0.05$)

Table II. *1 mg estriol vaginally.*

Patient	C_0		C_{24}	
	First day	21st day	First day	21st day
1	36	240	41	33
2	78	115	140	77
3	40	275	57	170
4	61	160	100	155
5	43	–	150	105
6	85	215	95	365
Mean	60	201 ($p < 0.05$)	86	160 (N.S.)

Table III. *Comparison of $AUC_{0\ 24\text{-}h}$ obtained after intravaginal and oral administration of estriol.*

Patient	1 mg estriol vaginally	10 mg estriol orally	Percentage decrease
1	4000	5033	−25.8
2	8906	19195	−115.0
3	7697	9184	−19.3
4	8972	6840	23.8
5	18634	11092	40.5
6	16091	6953	56.8
Mean	10716	9719	−7.8 (N.S.)

In patients one and 3, the plasma estriol elevation was steady for 12 hours. In patient 2, there was a second very high plasma estriol increase 4 hours after the oral estriol administration. The $AUC_{0\text{-}24\text{-}h}$ levels after vaginal administration of 1 mg estriol and oral administration of 10 mg estriol did not differ significantly (Table III). From the figures, it seems that the plasma estriol levels, when estriol was given orally, were influenced by ingesting a meal (Fig. 3). A meal 4 hours after the oral estriol administration induced a second plasma estriol increase lasting at least as long as the first one (Fig. 3).

None of the 6 volunteers noticed any inconvenience or any side effects during the 21-day treatment period with estriol given intravaginally. One woman (Figs. 1–3, patient 5) had a vaginal bleeding when treatment was completed. Curettage was done 3 weeks later. The histological examination of the specimen revealed an atrophic endometrium.

DISCUSSION

On vaginal administration of 1 mg estriol (ovula of estriol supplied by Leo Ab, Sweden), the absorption was found to be very effective. During daily treatment with 1 mg estriol intravaginally for 21 days, the absorption declines significantly (Figs. 1, 2, Table I). In spite of this, the plasma levels of estriol on vaginal administration of only 1 mg estriol are almost in the same range as the plasma estriol levels obtained with 10 mg estriol administered orally (tablets Triovex^R, Leo AB, Sweden) (Figs. 1–3, Tables I, III).

The somewhat reduced absorption during longterm vaginal treatment is possibly caused by the maturation of the vaginal epithelium induced by estriol. The mature vaginal epithelium does not, however, obstruct further absorption and hence does not prevent systemic effects of estriol.

A single daily dose of 10 mg estriol given orally is considered a high dosage in current therapy. With oral administration once a day, the same amount of estriol as was given in our study has been found to exert a clinical effect on the vasomotor instability and on the vaginal epithelium.

The good clinical effect of oral high dosage treatment can be attributed to the initial rise in plasma estriol levels, though rapidly declining yet followed by a second elevation possibly induced by a meal and depending on deconjugation and enterohepatic recirculation of estriol. This results in a prolonged elevation of estriol blood levels and a continuous stimulation of the estrogen receptors necessary for full estrogenic activity (1). This enterohepatic recirculation – and not the infrequent sampling, as stated earlier (2) – may be the explanation why Rauramo et al. (8) found the highest estriol concentration 12 hours after oral administration of 8 mg estriol succinate. The same phenomenon may also account for the good clinical effects of a daily single high dose estriol treatment as reported (10). Not only is the vaginal absorption of estriol more effective than the oral one as reflected by the plasma estriol elevation, but the concentration of unconjugated biologically active estriol is also higher. When corresponding doses of estriol are given vaginally and orally, a most striking difference is that the concentrations of conjugated estriol are 4–24 times as high after oral as after vaginal administration (9).

Since the unconjugated estrogen is believed to be biologically active, a more pronounced effect is conceivable, when estriol is administered vaginally and reaches the peripheral circulation, thus avoiding instantaneous and substantial conjugation due to first-pass effect in the liver. In favor of the assumption of a higher clinical effectiveness of vaginally versus orally administered estriol is also the effect on gonadotro-

pins (FSH) exerted by vaginally administered estriol. When equal amounts of estriol (4 mg) were given, the vaginal (but not the oral) route caused gonadotropin suppression (6).

Moreover, it is known from earlier studies that even a low dose of estriol given intravaginally is evidently sufficient to affect the endometrium (4), probably due to the effective vaginal absorption and the sustained plasma estriol elevation.

In this study, it is confirmed that a low dose of estriol given intravaginally is capable of inducing endometrial stimulation, while one subject (No. 5, Figs. 1–3) sustained vaginal bleeding when estriol treatment was carried out for more than 21 days. Hence, it is concievable that many more subjects would have sustained vaginal bleeding if the treatment period had been further prolonged.

CONCLUSION

The mode of estriol administration rather than the drug itself is one factor that determines whether or not the drug will have an estrogenic effect on the end-organs. Our data indicate that the vaginal absorption of estriol is more effective than the oral one, as the concentration of unconjugated estriol is higher. Due to the very effective conjugation of orally absorbed estriol, it appears that larger doses of estriol would have to be given orally rather than vaginally in order to achieve an equivalent effect (9).

After long-term treatment with estriol intravaginally, the absorption of estriol declines but is still nearly in the same range as after oral high dosage estriol regimen. Hence, the maturation of the vaginal epithelium seems not to obstruct estriol absorption during long-term treatment.

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Gun Heimer, M.D.
Kvinnokliniken
Akademiska Sjukhuset
S–751 85 Uppsala
Sweden