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Plasma oestriol following vaginal administration: morning versus evening insertion and influence of food

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The aim of this trial was to study the vaginal absorption of oestriol and to investigate whether morning rather than evening oestriol administration would produce different plasma oestriol patterns. The influence of food intake on plasma oestriol levels was also investigated.

Nine post-menopausal women were given 0.5 mg oestriol (ovula supplied by Leo AB, Sweden) intravaginally every evening for 16 days. Thereafter, 1 mg oestriol was given every evening for another 5 days, except on treatment days 18 and 19 when 1 mg oestriol was given in the morning instead. Venous blood samples were collected at frequent intervals on day 19 (morning administration) and a meal was allowed 4 h later. On the day 21 (evening administration), venous blood samples were taken at frequent intervals during the night and no meal was given until the next morning. Plasma concentrations of unconjugated oestriol were measured by means of a specific radioimmunoassay (RIA). A difference was seen in the plasma oestriol patterns when the results following morning and evening administration were compared. However, no significant difference as regards the total 24-h systemic availability of oestriol was observed. A minimal increase in plasma oestriol levels was seen after a meal in the case of both morning and evening intravaginal oestriol administration, possibly as a result of enterohepatic recirculation.

(Key words: Oestriol; Intravaginal, Morning/evening administration)

Introduction

Oestriol is considered to be a weak oestrogen because of its short binding time to the oestrogen receptor and its rapid metabolic clearance rate [1,2]. Previous studies have confirmed that oestriol is absorbed more effectively via the vaginal route [2–4] than the oral, and that this difference is maintained throughout prolonged treatment despite maturation of the vaginal epithelium [4]. A review of the literature on intravaginally administered oestriol revealed that only daytime trial results were available, whereas vaginal oestriol is probably most commonly used in the evening.

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Subjects and methods

Nine healthy, post-menopausal women aged 53–62 yrs gave their informed consent to participate in the study. None had had any vaginal bleeding for at least 2 yr or been on oestrogen therapy during the previous 6 mth. The participants were instructed to abstain from sexual intercourse during the last week of the trial. All had normal liver function tests and none had been cholecystectomised.

An ovulum containing 0.5 mg oestriol (Leo AB, Sweden) was inserted into the vagina every evening for 16 days. Thereafter, 1 mg oestriol was given in the same way for another 5 days. However, on days 18 and 19, the oestriol was given instead at 08.00 in the morning after an overnight fas. A peripheral venous blood sample was drawn immediately before and then $\frac{1}{2}$, 1, 2, 3, 4, $4\frac{1}{2}$, 5, 6, 8, 10, 12 and 24 h afterwards. No meal was allowed until 4 h after oestriol administration.

On day 21 of the treatment, 1 mg oestriol was given intravaginally at 21:00 in the evening. The women remained in hospital overnight and blood samples were drawn from an indwelling venous catheter without any disturbance of sleep. The participants were not allowed to eat or drink until 07:00 the next morning. A peripheral venous blood sample was drawn immediately before and then $\frac{1}{2}$, 1, $1\frac{1}{2}$, 2, 3, 4, 6, 8, 10, 11, $11\frac{1}{2}$, 12, $12\frac{1}{2}$, 13, 15, 19 and 24 h after oestriol administration. Plasma concentrations of unconjugated oestriol were measured using a specific radioimmunoassay (RIA) [5]. The plasma was withdrawn and stored at $-20°C$ until analysed. All samples were run in the same assay.

Wilcoxon's nonparametric test was used for statistical analysis. The areas under the plasma concentration vs. time curve (AUC_{0-12h}; AUC_{0-24h}) were calculated using the trapezoidal rule (Table I).

TABLE I

COMPARISON OF AUC_{0-12h} AND AUC_{0-24h} [a] AFTER INTRAVAGINAL ADMINISTRATION OF 1 MG OESTRIOL

Patient	AUC_{0-12h}		AUC_{0-24h}	
	Morning	Evening	Morning	Evening
1	4648.8	4226.3	5356.8	5697.3
2	1455.8	1633.8	1971.8	3073.5
3	2306.7	3039.5	3044.7	3582.0
4	14392.5	10180.0	17692.5	18818.8
5	6423.5	9771.8	13623.5	12444.3
6	8823.8	3598.8	16233.8	11636.3
7	11495.0	1899.0	15095.0	6334.0
8	3143.8	2743.8	6173.8	8233.8
9	797.0	5328.8	3977.0	8682.5
Mean	5943.0	4713.5	9941.0	8722.5
	NS [b]		NS	

[a] Areas under the plasma concentration versus time curve.

[b] NS, not significant.

Results

The mean plasma levels of unconjugated oestriol achieved after vaginal administration of 1 mg oestriol in the morning on day 19 and in the evening on day 21 are shown in Fig. 1. The individual oestriol absorption rates, as reflected by the plasma oestriol levels, were considerable after both morning and evening administration.

Following morning administration a rise in plasma oestriol was seen during the first 3–4 h. A meal given 4 h after oestriol administration was followed by a minimal plasma oestriol elevation. The plasma oestriol level subsequently remained stable for another 4 h and then slowly fell to almost the pretreatment value after 24 h. After evening insertion no initial plasma oestriol rise was seen during the first 3 h. A slowly increasing plasma oestriol level was then observed during the overnight fasting period and a further, minimal elevation was seen after the morning meal, 10 h after oestriol administration. Thereafter, the plasma oestriol concentration fell to almost the pretreatment level after 24 h.

The plasma oestriol pattern seen when oestriol was administered in the evening was different to that observed after morning administration. However, when the areas under the plasma vs. time curve (AUC_{0-12h}; AUC_{0-24h}) were calculated, it was found that the 24-h plasma oestriol elevation after morning administration did not differ significantly from that after evening administration (Table I).

None of the 9 volunteers reported any inconvenience or other side effects during the 21-day period of treatment with intravaginal oestriol.

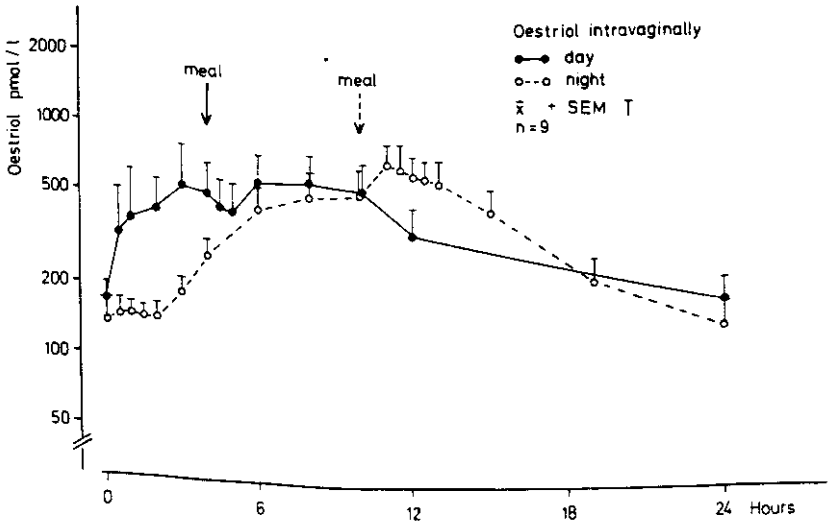

Fig. 1. Plasma levels of oestriol after intravaginal administration of 1 mg oestriol to nine women in the morning on treatment day 19 (continuous line) and in the evening on day 21 (broken line). The mean and SEM were calculated in each case.

Discussion

Women are usually instructed to insert oestriol ovula into the vagina in the evening at bedtime for the treatment of post-menopausal disorders. However, previous studies on intravaginally administered oestriol have reported results only after daytime insertion [6–8].

In our study a different plasma oestriol pattern was observed following morning rather than evening administration of intravaginal oestriol ovula. Morning administration resulted in an early plasma oestriol rise within 3–4 h, while evening administration produced no initial rise for the first 3 h. Instead, a slowly increasing plasma oestriol level was seen during the night. This prolonged plasma oestriol elevation may possibly result from slower metabolism during sleep.

These findings are in agreement with those reported in a study by Fink et al. [9] in which oestriol was administered vaginally and unconjugated plasma oestriol was measured over the following 6 h. The investigators reported a late plasma oestriol peak with a prolonged plasma oestriol elevation which still persisted in resting, recumbent women after 6 h, whereas in active, ambulant women an early plasma oestriol peak and a plasma oestriol elevation lasting for only 4 h was seen. The authors did not, however, discuss their findings further [9].

After both morning and evening oestriol administration, minimal plasma oestriol increases were seen following a meal. These were possibly a result of enterohepatic recirculation of oestriol, with deconjugation and reabsorption of unconjugated oestriol from the intestine into the bloodstream. Hence, when oestriol is administered intravaginally, enterohepatic recirculation may be a factor with contributes to the maintenance of elevated plasma oestriol concentrations. The need for further investigation of this aspect is clearly indicated. Enterohepatic recycling of oestriol resulting in plasma oestriol elevation following the intake of food has previously been demonstrated during oral oestriol treatment [10–12].

The vaginal absorption of oestrogens during long-term treatment has been a subject of some debate and certain investigators have suggested that absorption might be reduced in women with a mature vaginal epithelium [13]. In this study absorption through the vaginal epithelium was still found to be apparent on treatment days 19 and 21, despite the maturation of the vaginal epithelium induced by the oestriol.

Conclusion

A different plasma oestriol pattern was seen following morning as against evening intravaginal administration of oestriol, which might be explained by differences in the day and nighttime pharmacokinetics of this substance. However, there was no significant difference as regards the 24-h systemic availability of oestriol.

A minimal plasma oestriol elevation seemed to be induced by the intake of food, after both morning and evening oestriol administration, possibly as a result of

enterohepatic recirculation. The maturation of the vaginal epithelium induced by oestriol was not found to prevent its absorption during treatment with intravaginal ovula.

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