Rapid Absorption of Micronized Estradiol-17β Following Sublingual Administration

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The effect of sublingual administration of 2 mg of micronized estradiol-17β (E_2) on circulating concentrations of estrone (E_1), E_2, luteinizing hormone, and follicle-stimulating hormone was evaluated. Six women were studied during the early follicular phase, along with 3 hypogonadal women. Absorption of E_2 was extremely rapid with a respective 9-fold and 41-fold increase over basal serum levels within 30 minutes. However, for most of the 24-hour period studied, E_1 rather than E_2 was the predominant circulating estrogen. Although physiologic levels of E_2 can be maintained, it would appear that the sublingual route is not ideal for E_2 replacement, as concomitant superphysiologic elevation of circulating E_1 occurs. *(Obstet Gynecol 57:62, 1981)*

The oral administration of micronized estradiol-17β (E_2) to postmenopausal women produces a significant beneficial effect in relieving symptoms of estrogen deficiency. However, a preferential increase in circulating estrone (E_1) rather than E_2 is seen,[1] suggesting rapid interconversion of E_2 to E_1 by the mucosa of the small bowel.[2] Intravaginal administration of E_2, on the other hand, has been shown to result in rapid sustained elevation of serum E_2 levels in hypogonadal women.[3-5] Stable levels of both E_1 and E_2 can be maintained by daily vaginal application of E_2 cream.[6] In the search for an alternative route to achieve physiologic estrogen replacement, the authors examined serum E_1 and E_2 concentrations after sublingual administration of micronized E_2.

Materials and Methods

Six women with regular cycles who were in the early follicular phase (days 2 to 4) and 3 hypogonadal women (1 postmenopausal woman and 2 with premature ovarian failure) volunteered for study. None had received any form of estrogen for at least 2 months. Studies were initiated between 0800 and 0900 hours. A 2-mg tablet of micronized E_2 was placed under the subject's tongue and the time until complete disappearance of the tablet was recorded. Three basal samples of blood were drawn at 15-minute intervals from an antecubital vein before E_2 administration. After sublingual E_2 administration, blood samples were obtained at 5-minute intervals for the first 15 minutes, then at 15-minute intervals for 3 hours, 30-minute intervals for 2 hours, 60-minute intervals for 3 hours, and at 24 hours. A normal diet and activity were maintained during the study.

Serum E_1, E_2, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) were measured by radioimmunoassay.*[7-9] Statistical analyses were performed by the Student paired *t* test and analysis of variance.

Results

In all subjects, the sublingual tablet of micronized E_2 dissolved completely within 30 to 90 seconds. A chalky but not unpleasant taste was noted. Figure 1 shows the mean (± SE) basal and incremental levels of serum E_1 and E_2 in 6 women in the early follicular phase. Serum E_2 began to rise within 5 minutes of administration of micronized E_2 and reached a peak (432 ± 61 pg/ml) at 30 minutes, representing a ninefold increase over the basal level (50 ± 11 pg/ml). Thereafter E_2 levels dropped precipitously to approximately 100 pg/ml at 3.5 hours and returned to baseline at 24 hours. In contrast, serum E_1 levels began a slower but progressive rise within 10 minutes and surpassed E_2 levels at 1.5 hours. The peak concentration of 487 ± 55 pg/ml attained at 6 hours represented approximately

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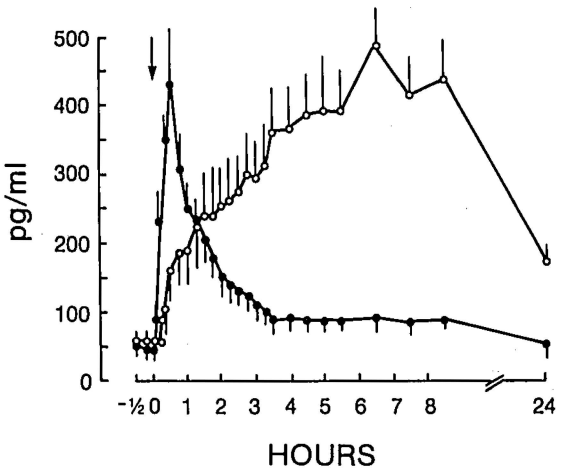

Figure 1. Mean (±SE) basal and incremental changes of serum E_1 (open circles) and E_2 (solid circles) following sublingual administration of 2 mg of micronized estradiol-17β to 6 subjects in the early follicular phase.

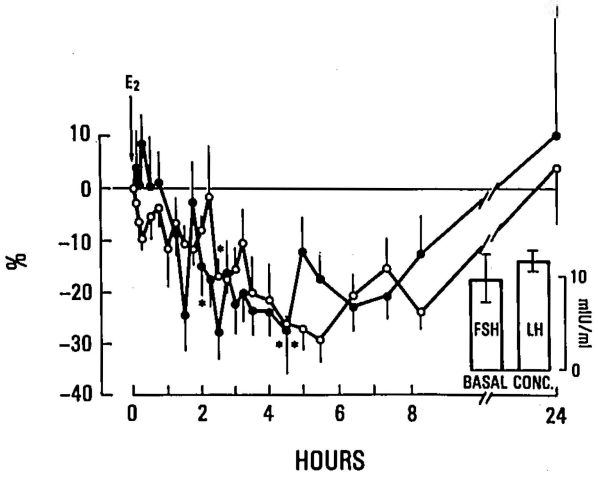

Figure 3. Percent change in FSH (open circles) and LH (solid circles) following sublingual administration of 2 mg of micronized estradiol-17β to 6 subjects in the early follicular phase. (*$P < .05$, **$P < .01$). Basal gonadotropin concentration is shown in the insert.

an eightfold rise over the basal level (56 ± 8 pg/ml). Serum E_1 was still significantly ($P < .05$) above the basal level at 24 hours (170 ± 30 pg/ml).

Mean (± SE) basal and incremental levels of serum E_1 and E_2 in 3 hypogonadal women are shown in Figure 2. Serum E_2 began to rise within 5 minutes of sublingual administration of micronized E_2 and reached a peak value (648 ± 66 pg/ml) at 45 minutes, a 41-fold increase over the basal level (15 ± 7 pg/ml). Serum E_1 increments progressively reached a peak (412 ± 108 pg/ml) at 5.5 hours, representing a 17-fold increase over the basal level (24 ± 2.2 pg/ml). The pattern of E_1 and E_2 increments is quantitatively and qualitatively similar to that for women with regular cycles.

Serum gonadotropin levels decline gradually following sublingual E_2 administration to women in the early follicular phase (Figure 3). Serum LH concentration was significantly ($P < .05$) below the basal level (10.4 ± 1.4 mIU/ml) by 2 hours. At 2.5 hours, serum FSH was significantly ($P < .05$) below the basal concentration (9.3 ± 2.5 mIU/ml). In 3 hypogonadal women (Figure 4), serum LH and FSH were significantly ($P < .05$) below the basal values (116 ± 13 and 162 ± 41 mIU/ml, respectively) at 1.75 hours.

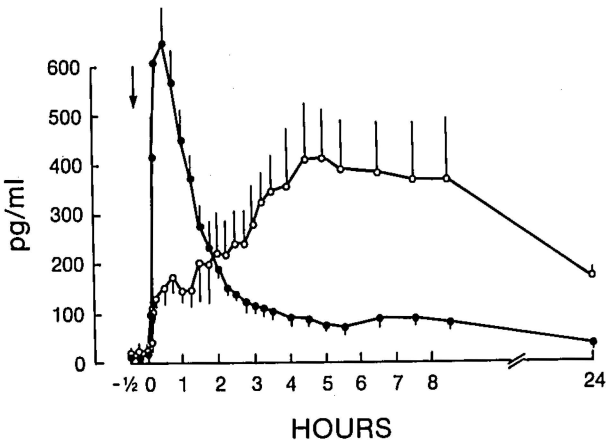

Figure 2. Mean (± SE) basal and incremental changes of serum E_1 (open circles) and E_2 (solid circles) following sublingual administration of 2 mg of micronized estradiol-17β in 3 hypogonadal subjects.

Discussion

The authors have demonstrated the rapid sublingual absorption of micronized E_2. The pattern of absorption is similar to that of an intranasally applied E_2 suspension.[3] As seen also in oral E_2 ingestion,[1] E_1 rather than E_2 is the predominant serum hormone achieved. The rich venous drainage of the sublingual area[10] probably accounts for the initial rapid increase and the precipitous decline of circulating E_2. The progressive rise in serum E_1, reaching a peak at 5 to 6 hours, is suggestive of storage and conversion of E_2 to E_1 at some tissue site followed by slow release. Whether this in fact occurs is unknown, but it is tempting to speculate that the rich lymphatic drainage of the sublingual area to the deep cervical nodes[10] may be involved. A significant contribution of the lymphatic system in the sublingual absorption of paraaminosalicylic acid has been demonstrated in rabbits following occlusion of the esophagus, trachea, and jugular veins bilaterally.[11]

Unlike oral ingestion, both the sublingual and vaginal routes of estrogen administration may circumvent the portal circulation and thus avoid high hepatic uptake of estrogen. A potential advantage is the pre-

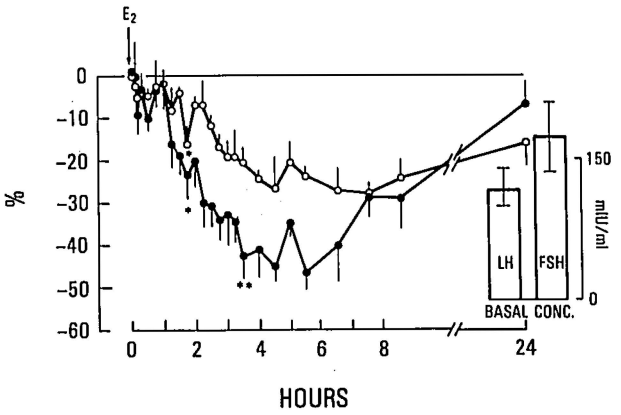

Figure 4. Percent change in FSH (open circles) and LH (solid circles) following sublingual administration of 2 mg of micronized estradiol-17β in 3 hypogonadal women ($^*P < .05$, $^{**}P < .005$). Basal gonadotropin concentration is shown in the insert.

vention of liver adenomata, which has been reported following the prolonged oral use of estrogen preparations.[12]

The sublingual route does not appear to be ideal for E_2 therapy, either replacement or contraceptive. Unlike the intravaginal route in which E_2 is absorbed unchanged,[3-5] the sublingual route results in higher serum concentrations of E_1 than of E_2. However, the sublingual route of administration may be applicable for hormones such as peptides, which would be rapidly inactivated if ingested.

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