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VAGINAL ABSORPTION OF ESTRONE AND 17β-ESTRADIOL*†

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In order to study estrogen absorption from the vagina, 0.5 mg of unconjugated estrone (E_1) or 17β-estradiol (E_2) was administered vaginally to 10 postmenopausal patients. A 29-fold increase in plasma E_2 and a 4-fold increase in plasma E_1 concentrations were observed 1 hour following the vaginal deposition of 0.5 mg of E_2. Maximal decreases of 25% and 37% in plasma levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), respectively, were observed at 5 hours following treatment. One hour after vaginal administration of 0.5 mg of E_1, a 24-fold increase in plasma E_1 and a 3.7-fold increase in E_2 were observed. These increases were associated with a 30% decrease in plasma FSH and LH. These data indicate that the vaginal administration of E_2 or E_1 may be used to achieve physiologic blood levels of these estrogens. They further suggest that vaginal estrogens not be used in patients in whom systemic estrogen therapy is contraindicated.

17β-Estradiol (E_2) is the predominant estrogen of ovulating women.[1] The desire to achieve physiologic levels of E_2 in the blood of patients requiring estrogen replacement has been hampered by lack of suitable means of administration. Ryan and Engel[2] have shown that the gut converts E_2 into estrone (E_1). Yen et al.[3] demonstrated that the oral administration of micronized E_2 results in a more marked increase in circulating E_1 than in E_2. The subcutaneous instillation of E_2, although effective, is not practical.[4] It has long been known that estrogens can be readily absorbed from the vagina in levels sufficient to produce endometrial stimulation and bleeding.[5] More recently, Widholm and Vertiainen[6] found that menopausal women treated with sodium estrone sulfate vaginally had urinary excretion values of estrogens which were equivalent to those of reproductive, ovulating women. Since the vaginal mucosa is not known to contain a very active oxidoreductase system,[7] it was logical to attempt the vaginal application of E_2 and E_1 in order to obtain physiologic levels of these estrogens.

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MATERIALS AND METHODS

Ten healthy postmenopausal patients with a mean age of 65 years (range, 50 to 91) volunteered to participate in the study. All of the women had symptoms of vaginal atrophy and displayed decreased rugae of the vaginal mucosa. None of the patients had any ulcerations. Only two of the volunteers complained of vasomotor flushes, and incidentally were the only ones who had had a previous total abdominal hysterectomy and bilateral salpingo-oophorectomy (for benign disease). None of these women had received exogenous estrogens for at least 1 month prior to entering the study, and all signed an informed consent. Five patients received 0.5 mg of micronized E_2 vaginally and the other five received 0.5 mg of E_1. The E_2 solution was prepared by dissolving 1 mg of micronized E_2 (Mead Johnson

Laboratories, Evansville, Ind.) in 4 ml of normal saline. Aliquots (2 ml) of this solution (0.5 mg) were then applied to the posterior fornix of the vagina. The E_1 solution, delivered in the same way, was made by dissolving 0.5 mg of crystallized E_1 (purity greater than 99%) in 3.5 ml of 12% ethanol in water. The E_2 solutions, when subjected to chromatography and analyzed by radioimmunoassay,[8] did not contain any detectable amounts of E_1 (<0.1%). The patients, who arrived at the menopausal unit at 8:00 A.M., were asked to remain recumbent for the 1st hour after the vaginal deposition of the estrogens. Afterward, they were allowed to move about and to eat ad libitum. Blood samples were obtained at 30 minutes and 1 minute prior to the vaginal application of E_1 or E_2 and then hourly thereafter for a total of 6 hours. The blood was centrifuged and the serum was frozen at −20° C until analyzed. Plasma levels of unconjugated E_1 and E_2 were measured by radioimmunoassay following Celite chromatography.[8] Plasma levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) were measured by radioimmunoassay.[9]

RESULTS

The effect of the vaginal deposition of 0.5 mg of E_2 on the plasma concentrations of E_1, E_2, FSH, and LH is shown in Figure 1. The mean (± standard error) basal E_2 of 30 ± 5 pg/ml increased 29-fold at 1 hour, reaching levels of 860 ± 247 pg/ml. Plasma E_2 concentrations remained in the 800 to 900 pg range for another 2 hours, after which they began to decrease. At 6 hours the mean plasma E_2 concentration of 244 ± 85 pg/ml was still 8-fold higher than pretreatment levels. The vaginal administration of E_2 had only a modest effect on plasma E_1 levels. Mean plasma E_1 concentrations increased gradually during the first 3 hours following the administration of E_2, to reach maximal levels of 208 ± 39 pg/ml—4 times higher than pretreatment levels (54 ± 14 pg/ml). At 6 hours they fell to levels of 130 ± 12 pg/ml, which were only 2.4-fold higher than pretreatment values. The effect of the vaginal administration of E_2 on plasma LH and FSH was maximal at 3 to 5 hours following E_2 treatment. The mean FSH and LH levels at 3 hours postinfusion (101 ± 10 mIU/ml and 53 ± 9 mIU/ml) were 13% and 37% lower than preinfusion levels, respectively ($P < 0.05$). At 5 hours post-treatment the FSH level of 92 ± 9 mIU/ml and the LH level of 53 ± 12 mIU/ml

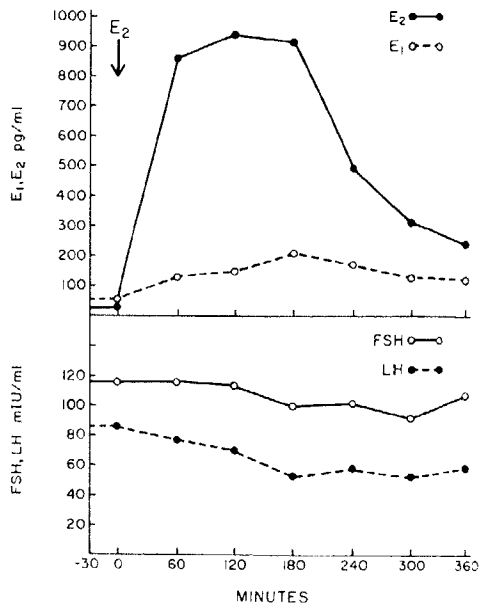

FIG. 1. Plasma E_1, E_2, LH, and FSH concentrations before and after the vaginal administration of 0.5 mg of micronized E_2.

were 25% and 37% lower than pretreatment ($P < 0.05$).

The effect of the vaginal administration of 0.5 mg of E_1 on the plasma concentrations of E_1, E_2, LH, and FSH is shown in Figure 2. At 1 hour post-treatment, the mean basal E_1 value of 30 ± 7 pg/ml increased 24-fold to reach levels of 733 ± 144

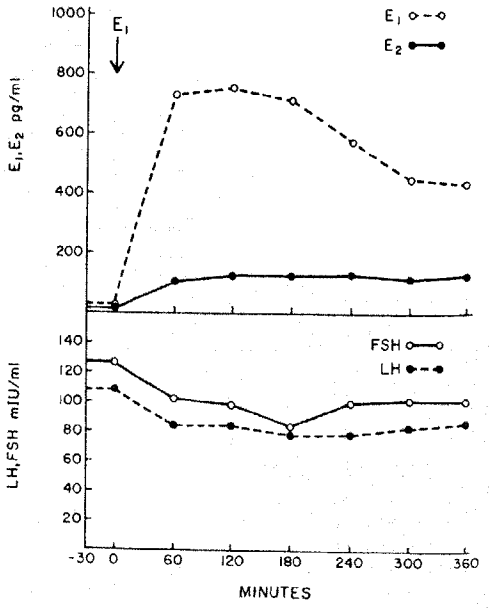

FIG. 2. Plasma E_1, E_2, LH, and FSH concentrations before and after the vaginal administration of 0.5 mg of E_1.

pg/ml. These high E_1 values were maintained for another 2 hours, after which they declined. At 6 hours, the mean plasma E_1 level of 435 ± 187 pg/ml was still 14-fold higher than pretreatment levels. At 1 hour the mean plasma E_2 level of 105 ± 24 was 3.7-fold higher than the pretreatment level (28 ± 8 pg/ml), and in the subsequent 5 hours the mean remained elevated at levels which ranged from 118 to 135 pg/ml. A significant decrease of 30% in plasma FSH and LH concentrations ($P < 0.05$) was noted at 3 hours following treatment; these levels remained suppressed for the next 3 hours.

None of the patients noted any improvement in their symptoms, nor did anyone complain of breast tenderness, nausea, or vaginal bleeding.

DISCUSSION

This study has demonstrated that estrone and 17β-estradiol are readily absorbed from the vagina, resulting in plasma levels higher than basal for at least 6 hours following their application. Moreover, the plasma E_2 levels reached following vaginal administration of 0.5 mg of micronized E_2 were 10-fold higher than those achieved following the oral administration of 4 times this dose.[3] The 0.5-mg dose of E_2 administered vaginally approximates the daily production rate of E_2 at the midcycle preovulatory peak.[10] The finding that the maximal plasma E_2 concentrations observed following vaginal E_2 application were approximately twice the peak E_2 levels reached at midcycle[11] could be explained by the rapid absorption of vaginal E_2 during the first few hours after its administration. These results are in agreement with those obtained by Dr. S. S. C. Yen.[12] Although the oral administration of E_2 is accompanied by a high rate of conversion of E_2 to E_1, this did not occur after vaginal administration of E_2. The relatively small, but significant, elevation of plasma E_1 could largely be accounted for by peripheral conversion of E_2 into E_1.[13] The vaginal administration of E_2 has an advantage over the oral route in that desired plasma E_2 levels may be achieved without an accompanying undesirable increase in E_1 to nonphysiologic levels. When E_1 was applied to the vagina, plasma E_1 rose promptly, reaching levels which were 3.5-fold higher than those observed at midcycle.[14] Again, relatively little change in plasma E_2 concentration was noted following vaginal E_1 administration.

In both groups of women, the estrogens absorbed were biologically active, as indicated by the significant decrease in plasma LH and FSH concentrations. It is of interest that in our study the fall of plasma LH and FSH following the vaginal administration of E_1 was of the same magnitude as that observed after vaginal administration of E_2. The decreases in plasma LH and FSH levels following the vaginal application of E_2 were also of the same magnitude as those reported following 3 hours of intravenous infusion of 0.4 mg of E_2.[10] These data suggest that the vaginal administration of E_2 can be used to achieve physiologic blood concentrations of E_2. Furthermore, they suggest that vaginal estrogens not be used in patients in whom systemic estrogen therapy is contraindicated.

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