The rickets of familial hypophosphatemia may be healed, and the growth pattern improved by large doses of buffered, isotonic phosphate solution (usually, 2 to 3 g of phosphorus phosphate daily). Ordinarily, concurrent vitamin D therapy is necessary to prevent the chronic high phosphate intake from inducing secondary hyperparathyroidism.

Acute administration of 1.5 g of orthophosphate stimulates the secretion of parathyroid hormone in human beings, and chronic administration of large doses increases bone resorption in experimental animals. Whether a high dietary phosphate intake predisposes to the development of osteoporosis remains to be established.

Other Nutritional Problems

Severe calorie and protein malnutrition leads to stunting of growth. Deficiency of vitamin C produces scurvy and is associated with subperiosteal and intramedullary hemorrhages and sometimes osteopenia. Vitamin A intoxication can cause cortical hyperostosis in infants and children and increased bone resorption in adults.

Finally, excessive fluoride ingestion — usually occurring when its concentration in drinking water exceeds 20 ppm — leads to osteosclerosis and occasionally to exostosis and ligamentous calcification and to neurologic signs because of bony overgrowth.

Therapy with sodium fluoride and calcium has been shown to increase formation of normally mineralized bone in osteoporotic patients.[11] The safety of long-term treatment and its efficacy in reducing the incidence of further vertebral fractures deserve further study.

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ABSORPTION OF ESTROGENS FROM VAGINAL CREAMS

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INTRAVAGINAL application of estrogen-containing creams has been widely used in the treatment of vaginal atrophy and related conditions due to estrogen deficiency. Although its efficacy is well recognized,[1,2] the assumed "topical" effect and the potential for absorption of estrogenic substances contained in the vaginal cream are virtually unexplored.

Recent observations indicate that the efficacy of absorption of micronized 17β-estradiol yields blood estradiol levels 100 times higher when administered intravaginally in salines than when given by mouth.[3,4] Moreover, the substantial intestinal conversion of estradiol to estrone, observed after oral administration of estradiol,[3] is circumvented by intravaginal application. These findings prompted us to examine the quantitative absorption of estrogens after intravaginal application of estrogen-containing creams.

Materials and Methods

The usual prescribed dose of 2 g of vaginal cream containing 1.25 mg of conjugated estrogens (Premarin) administered with a vaginal applicator was used in the present study. The conjugated estrogens contained in the preparation are a mixture of estrone sulfate (70 per cent) and equilin sulfate (20 per cent), together with small amounts of equilenin sulfate and the 3,17-diols of those steroids.[5]

Micronized 17β-estradiol vaginal cream (Estrace vaginal cream) was prepared in two concentrations and supplied by the Mead Johnson Company, Evansville, Indiana. The nonliquefying cream base in this preparation is identical to that of vaginal cream containing conjugated estrogen. For this study, a 2-g vaginal application containing either 2.0 or 0.2 mg of estradiol was administered and compared with a 1.25-mg dose of conjugated-estrogen cream.

Six estrogen-deficient women volunteered for this study. Informed and written consents were obtained. None of the subjects had received any form of estrogen treatment or other type of medication for at least four weeks before this study. Their mean ($\pm$ S.E.M.) basal hormone concentrations were as follows: estradiol, 14.1$\pm$0.9 pg per milliliter; estrone, 27.5$\pm$1.2 pg per milliliter; follicle-stimulating hormone, 101$\pm$3.3 mIU per milliliter; and luteinizing hormone, 105$\pm$8.3 mIU per milliliter.

The three creams were tested in each subject with the sequence determined by a Latin-square design. At least four days elapsed between tests in any given subject. On the morning of each experiment, two basal blood samples were obtained at 15-minute intervals. After the intravaginal application of an estrogen cream, blood samples were drawn at 15 minutes, 30 minutes and one, two, three, four, six, eight, 12 and 24 hours. Serum concentrations of estradiol, estrone, follicle-stimulating hormone and luteinizing hormones were determined by radioimmunoassay.[6-8] Statistical analyses were performed by the Student's paired t-test or group t-test as appropriate.

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Results

Basal estrone and estradiol levels did not vary significantly during the course of this study, indicating the complete disappearance of exogenous estrogens from previous experiments. The time course and incremental changes of circulating estradiol and estrone after the intravaginal application of the three preparations are shown in Figure 1. Circulating levels of estradiol were significantly ($P<0.05$) elevated within 15 minutes after the intravaginal administration of estradiol cream in the 2-mg dose, and the mean peak concentration of 527±45 pg per milliliter (S.E.M.) was reached at four hours, representing nearly 45 times the mean basal estradiol level. Thereafter, levels decline slowly but remain 19 times higher (263±114 pg per milliliter) than the basal level at 24 hours.

With the low-dose estradiol cream (0.2 mg) circulating estradiol was significantly elevated ($P<0.01$) at 30 minutes; the peak level of 6.8 times (80±19 pg per milliliter) the basal value was also attained at four hours. This increase was followed by a progressive decline to 34±9.8 pg per milliliter at 24 hours, which is still more than two times higher than the basal concentration.

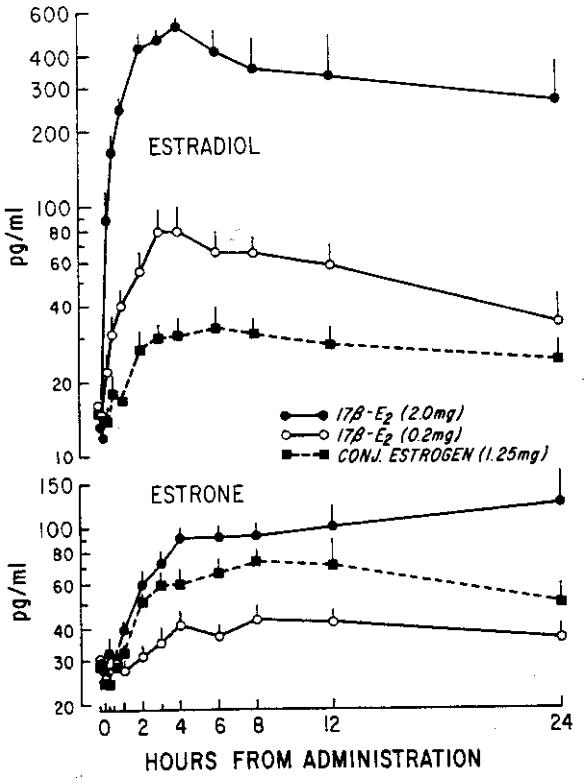

Figure 1. Basal Serum Concentrations (Mean ± S.E.M.) of Estradiol (E_2) and Estrone and Their Incremental Changes after Intravaginal Application of E_2 Cream at 2.0-Mg and 0.2-Mg Doses as Compared with 1.25 Mg of Conjugated-Estrogen Cream in Six Hypogonadal Women with Severe Estrogen Deficiency (Note that the Estrogen Concentrations are Plotted on a Log Scale).

In contrast, the intravaginal application of conjugated-estrogen cream (1.25 mg) resulted in a slower rise and much lower peak concentration of circulating estradiol (Fig. 1). A statistically significant elevation of estradiol did not occur until the third hour ($P<0.01$), and the mean peak level (33±6.6 pg per milliliter) reached at the sixth hour was only 2.5 times the basal level. By 24 hours, estradiol concentrations were higher but not significantly different from the basal level. When incremental changes of estradiol levels were compared among the three preparations of vaginal creams, the differences were significant ($P<0.01$ to $P<0.006$) at all intervals studied except between 0.2 mg of estradiol and 1.25 mg of conjugated estrogen at 24 hours (Fig. 1).

With the 2-mg dose of estradiol cream, serum estrone was significantly ($P<0.04$) elevated above basal level at one hour, increasing progressively thereafter for at least 24 hours (Fig. 1). With 0.2 mg of the cream, serum estrone levels were not significantly elevated until the third hour ($P<0.02$) and reached a peak concentration (43±5.5 pg per milliliter) of 1.6 times the basal level at the eighth hour. By 24 hours, the mean estrone level was no longer significantly different from the basal level. In distinct contrast, 1.25 mg of conjugated-estrogen cream induced a greater incremental change of serum estrone than estradiol. A significant elevation of estrone occurred at two hours ($P<0.03$), and the peak level (73±9.2 pg per milliliter) was reached at eight hours. The subsequent decline was slow, and the levels at 24 hours (50±8.7 pg per milliliter) were almost twice the basal levels.

The decline in serum luteinizing hormone and follicle-stimulating hormone was greater with estradiol vaginal cream at both doses than with conjugated-estrogen vaginal cream (Fig. 2). Follicle-stimulating hormone was significantly suppressed at eight hours ($P<0.002$) for the 2-mg as well as for the 0.2-mg estradiol cream and at 12 hours for conjugated-estrogen cream. The percentage of suppression was greater for luteinizing than for follicle-stimulating hormone. A significant decline of luteinizing hormone occurred at three to four hours for all three preparations ($P<0.02$), but, quantitatively, the conjugated-estrogen vaginal cream induced the least gonadotropin suppression.

Discussion

The present study demonstrates that conjugated estrogens, as well as the 17β-estradiol admixed with a cream base, can be readily absorbed by the vaginal mucosa in estrogen-deficient women. A prompt elevation of circulating estrogens occurs after a single intravaginal application of all three estrogen-contain-

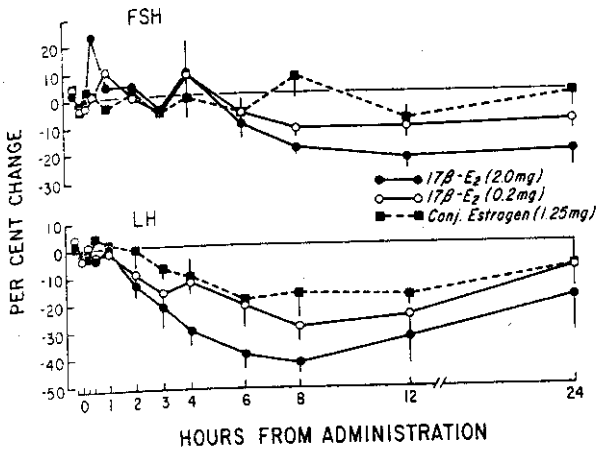

Figure 2. Basal Concentrations (Mean ± S.E.M.) of Follicle-Stimulating Hormone (FSH) and Luteinizing Hormone (LH) and Their Percentage Changes after the Intravaginal Application of the Three Estrogen-Containing Creams.

ing creams tested. However, the time course and the incremental changes in estradiol and estrone appear to be related to both the dose and the type of estrogen cream used. Thus, with both 2.0-mg and 0.2-mg doses of micronized estradiol vaginal cream, circulating estradiol exceeds the estrone levels, and a more sustained level is achieved with a larger (2.0 mg) than with the smaller (0.2 mg) dose (Fig. 1). In contrast, the cream containing conjugated estrogen (1.25 mg) produces a greater increment of estrone than of estradiol (Fig. 1). As expected, the largest estradiol increments with the 2-mg dose of estradiol cream is accompanied by the greatest degree of gonadotropin suppression and the least with conjugated-estrogen cream.[9,10]

The relatively smaller increments of serum estrone levels as compared to estradiol levels seen after estradiol vaginal cream are quantitatively similar to our earlier observations on the intravaginal application of micronized estradiol suspended in saline.[4] The appearance of increments of circulating estrone after both 2.0-mg and 0.2-mg doses of estradiol vaginal cream can be accounted for by the endogenous conversion of estradiol to estrone.[11,12] With the conjugated-estrogen cream, containing mainly estrone sulfate,[5] the incremental changes in circulating estrone probably reflect the cleavage of sulfate after the absorption of estrone sulfate, and the subsequent back conversion of estrone to estradiol may account for the small increments of circulating estradiol.[11,12]

The cream vehicle appears to retard the vaginal absorption of micronized estradiol. The levels of estradiol and estrone attained with the 2-mg dose of estradiol cream are achieved with the application of one-fourth (0.5 mg) the amount of micronized estradiol suspended in saline.[4] In either case, these estrogen levels are clearly supraphysiologic. However, with the 0.2-mg dose of estradiol in a cream, a near physiologic concentration of the hormone (80±8.5 pg per milliliter) is attained with a proportionally smaller rise of estrone (41±3.8 pg per milliliter) owing to the limited substrate for conversion. These levels of estradiol and estrone are essentially those of the follicular phase in women with normal cycles.[8] Thus, intravaginal application of micronized estradiol cream at the 200-μg dose may be considered physiologically appropriate for estrogen replacement in deficiency states.

It is clear that the biologic effect of intravaginally administered estrogen cream is mediated principally through delivery to target cells by the circulation. The assumed topical effect, if present, should be relatively small. Thus, caution must be exercised when vaginal estrogen cream is used to manage estrogen deficiency in the presence of estrogen-dependent neoplasms.

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