Pharmacokinetics of Oral 17 β-Estradiol

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The pharmacokinetics of oral 17 β-estradiol (E_2) were evaluated: only a limited amount of information is available on the subject. Because of the first passage hepatic effect, the blood levels of estrone (E_1) are greater than those of E_2; similar profiles exist for oral E_1 sulfate, micronized E_2 and E_2 valerate. However, the short-term effects of oral E_2 versus E_1 on hepatic parameters may vary somewhat. Peak levels of E_1 and E_2 are achieved four hours after the administration of 1 mg of E_2 and average 200 and 40–50 pg/mL, respectively. A dose-response relationship exists for serum levels achieved after oral E_2 administration. Twelve-hour values are representative of the 24-hour profile. With prolonged use, the 24-hour levels may be equally representative and serum E_2 levels increase, suggesting some cumulative effects. Smoking enhances the hepatic metabolism of oral estrogen and results primarily in a lower unbound E_2 level.

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Introduction

Reviewing the pharmacokinetics of oral 17 β-estradiol (E_2) is important because only a limited amount of information is available on the levels of E_2 and estrone (E_1) achieved in the circulation after oral administration. One of the goals of estrogen replacement therapy is to achieve physiologic levels of estrogen with oral therapy. Also, the knowledge of blood profiles of estrogen with frequent blood sampling will help determine the necessity for multiple or single doses of oral estrogen.

Routes of Administration

There are many ways in which E_2 can be delivered. For oral E_2 to be absorbed efficiently from the gastric mucosa, it needs to be administered in a micronized or conjugated form. The most common conjugated form of E_2 is E_2 valerate (E_2V), which, as discussed below, is extremely similar to micronized E_2 (Estrace). Unconjugated E_1 and E_2 are absorbed very inefficiently from the gastrointestinal tract. The vaginal mucosa, however, absorbs E_2 and E_1 in an extremely efficient manner,[1] and it has been suggested that E_2 is better absorbed vaginally than is E_1. Even whole tablets of micronized E_2 are well absorbed directly from the vaginal mucosa.[2] Other E_2 products include a transdermal preparation or patch and a percutaneous gel or cream. E_2 pellets or implants that deliver E_2 subcutaneously, directly into the systemic circulation, are also available.

E_2 is metabolized into E_1 as well as E_1 sulfate (E_1S).[3] Approximately 15% of E_2 is converted into E_1, and approximately 65% of E_2 is converted into E_1S (Figure 1). E_1S serves as a large, stable pool of estrogen within the circulation. There is a limited amount of back conversion of E_1 and E_1S into E_2. Only 5% of the E_1 in the blood is converted to E_2, and no more than 1.4% of E_1S is converted to E_2. Therefore, the overall fate of E_2 is toward metabolization into E_1 or E_1S. Although sulfates of E_2 and estriol also exist, the levels of those compounds are much lower.[4]

There is, however, more interconversion between E_1 and E_1S. Some 54% of E_1 is converted to E_1S, but E_1 also can be produced through a breakdown of E_1S. Approximately 21% of E_1S can be broken down into E_1. Estrone in the blood is metabolized by 16- and 2-hydroxylation, forming estriols and catecol estrogens, which are excreted primarily in urine.

How is estrogen metabolized within the cell? There are clear differences between blood and cellular estrogen metabolism. First, as depicted in Figure 2, regardless of whether E_2 or E_1 is administered orally, E_1 is

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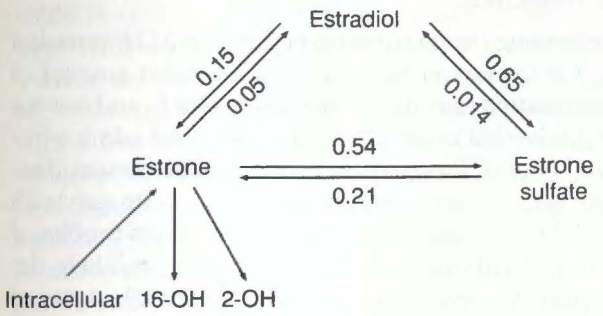

Figure 1
Estradiol metabolism.

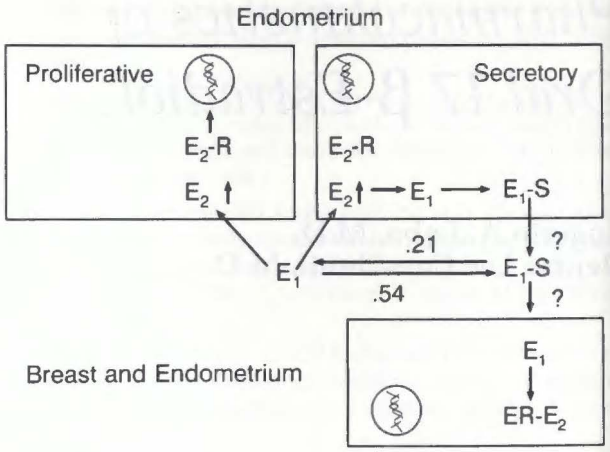

Figure 2
Estrone (E_1), estradiol (E_2) and estrone sulfate (E_1S) interaction in tissues.

the predominant estrogen in the circulation. However, when E_1 is taken up by cells, it is converted primarily to E_2. It has been shown that the principal intranuclear estrogen is E_2.[5] In the secretory endometrium, under the effects of progesterone, E_2 is converted through 17 β-E_2 dehydrogenase to E_1 and then is sulfurylated to E_1S. This step essentially deactivates the potency of E_2 in the cell, and E_1 may exit into the circulation.

As discussed above, E_1 and E_1S may be interconverted in blood. Although not completely established, E_1S also may be taken up by cells, such as in the breast, where sulfatase activity is able to liberate E_1 and E_2 in turn (Figure 2).[6,7]

Oral and Systemic Routes of Administration

E_1 is the predominant estrogen in the circulation after any oral preparation is administered (Figure 3). That is because of enhanced hepatic metabolism, or the first passage uptake effect, which occurs with oral administration. When E_2 is ingested, the liver actively deactivates E_2 by its metabolism into E_1 and E_1 conjugates. Some estrogen does enter the systemic circulation as E_2. However, E_1 is the predominant estrogen after oral E_2 administration, and the metabolites of E_1—E_1S and, more specifically, E_1 glucuronide (E_1G)—serve as markers of this first passage hepatic interaction. This hepatic effect results in the production of hepatic globulins as well as lipoproteins, such as high density lipoprotein (HDL) cholesterol.

E_2 administered systemically is converted to E_1 in blood, but the effects on the liver are only secondary, and therefore the effects of hepatic globulins and HDL cholesterol are far less pronounced.[8] That E_1G is an important marker of the first passage effect of oral administration is illustrated in Figure 4. Within three hours there is approximately a threefold increase in serum E_1G with oral administration of E_2V. That does not occur, however, with the systemic forms, in which serum E_1G levels remain low.[9]

Once in the circulation, both E_1 and E_2 will express estrogen-related effects on the brain, cardiovascular system and bone. That is a reflection of the levels of E_1 and E_2 achieved and is independent of whether the estrogen is derived from oral or systemic administration. However, it is well known that E_2 is more potent than E_1, and it can be estimated that the levels of E_1 in blood required to equal the biologic effects of E_2 are at least threefold greater.

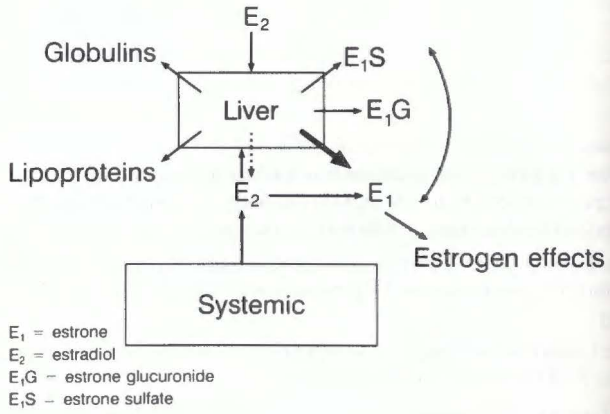

Figure 3
Oral versus systemic estradiol delivery.

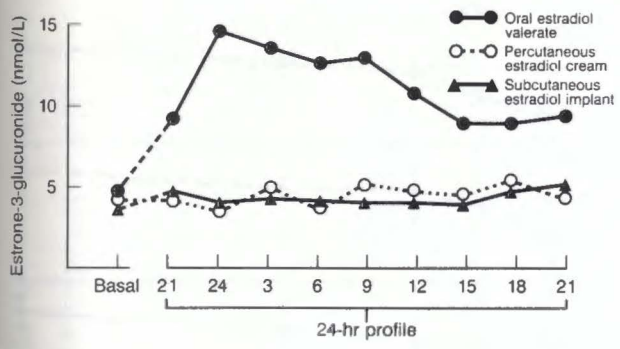

Figure 4
Levels of estrone-3-glucuronide after the administration of oral estradiol valerate and percutaneous estradiol cream and implantation of subcutaneous estradiol. From Siddle N et al, Contemp Obstet Gynecol 22:137, 1983.[9]

Comparison Between the Levels of Estrogen Achieved After Oral E_2 and E_1 Administration

E_2 is better absorbed in its conjugated or micronized form; the same is true of E_1. Therefore, E_1 usually is administered as the conjugate, E_1S. A study by Anderson[10] compared the levels of serum E_1 and E_2 after the administration of 1.5 mg of oral piperazine E_1S and 2 mg of E_2V. The serum levels of E_2 achieved were nearly identical (Figure 5). Although the pharmacokinetics were similar, E_2V administered at a higher dose, 2 mg as compared with 1.5 mg of E_1S, resulted in levels of E_1 that were slightly higher. Serum E_1S levels after E_2V and E_1S were again almost superimposable (Figure 6). Peak levels of E_2, E_1 and

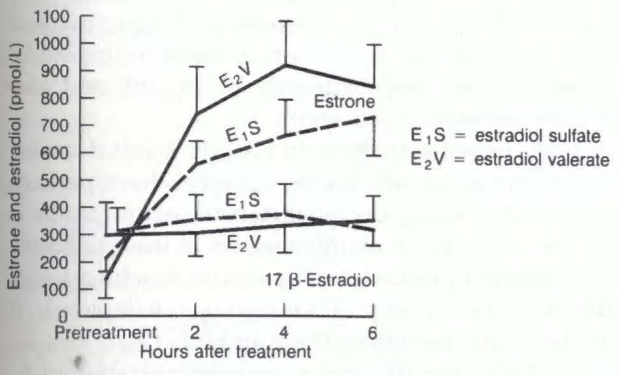

Figure 5
Mean serum concentrations of estrone and 17 β-estradiol before and at two-hour intervals after the administration of 1.5 mg of oral piperazine estrone sulfate and 2 mg of estradiol valerate in postmenopausal women. From Anderson ABM et al, Br Med J 1:140, 1978.[10]

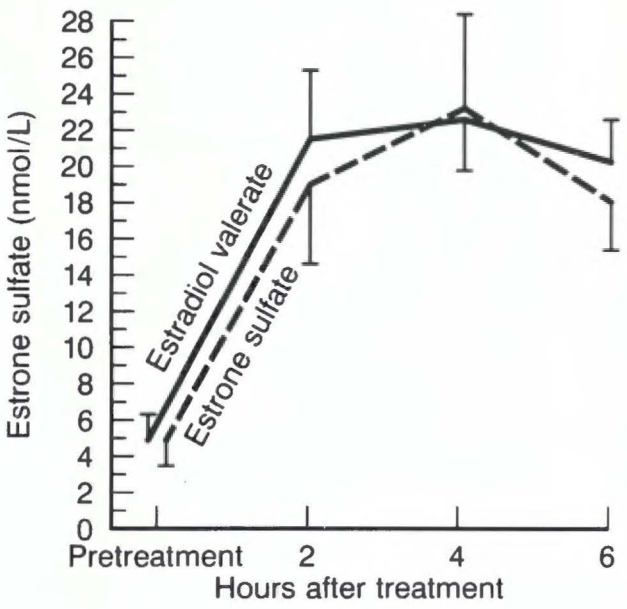

Figure 6
Comparison of estrone sulfate levels after estradiol valerate and estrone sulfate administration. From Anderson ABM et al, Br Med J 1:140, 1978.[10]

E_1S occurred at approximately four hours with each preparation.

The administration of 1 and 3 mg of piperazine E_1S also suggests a linear dose-response relationship in the pharmacokinetics of E_1S administration (Figure 7). Serum levels that peak at four hours were seen in one study[10] to be maintained for many hours. The data suggest that the half-life of E_1S is approximately 12 hours.[10] Other studies that have compared the pharmacokinetics of E_2V and E_1S also have suggested similar half-life characteristics.[11] The studies to date, therefore, suggest that in terms of E_2 and E_1 levels achieved in the circulation after oral therapy, there are no real differences between the oral administration of equal doses of the conjugated forms of the two.

Whether there are biologic differences between the effects of E_2 and E_1 administered orally remains unclear. A recent study by Colvin et al[12] suggested that with an incremental oral regimen after the highest dose of estrogen, which was either 2.5 mg of E_1S (Ogen) or 2 mg of oral micronized E_2 (Estrace), there was a greater increase in HDL cholesterol after the E_2 was administered. While the two doses achieved the same serum concentrations of E_1 and E_2, there was a greater increase in HDL cholesterol and a greater reduction in low density lipoprotein cholesterol with

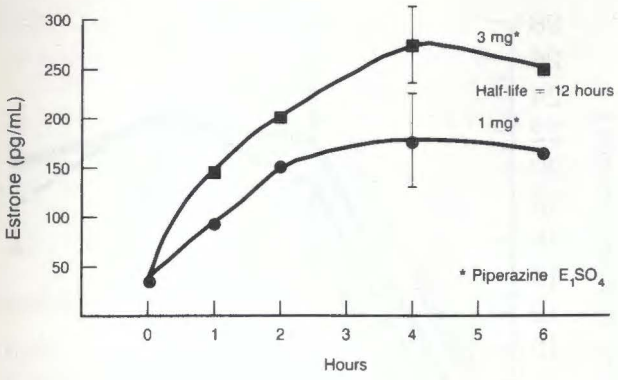

Figure 7
Levels of estrone after two doses of estrone sulfate. From Anderson ABM et al, Br Med J 1:140, 1978.[10]

E_2 than with piperazine E_1S (Figure 8). These results suggest that with oral administration there may be some subtle biologic differences related to inherent differences in the potency of E_2 and E_1. Clearly, more work is needed in this area.

Pharmacokinetics of Oral 17 β-E_2

With oral administration of 1 mg of β-E_2, serum levels of E_1 and E_2 increase rapidly during the first four to eight hours after ingestion.[13] Although interpatient variation exists, peak levels are attained by four hours. The levels of E_1 achieved are approximately 200 pg/mL, and the levels of E_2 are 40–50 pg/mL. In response to this oral dose, levels of E_1G peak within the first hour and then gradually return to normal. There is a slower, more gradual increase in E_1S, which again appears to peak at approximately four hours

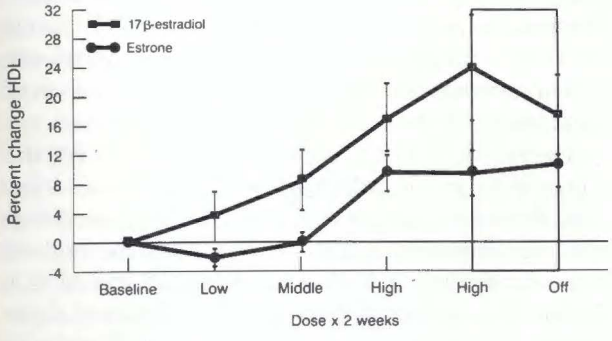

Figure 8
Percentage change in high density lipoprotein cholesterol from baseline concentrations to low, middle and high doses of 17 β-estradiol and estrone sulfate. From Colvin P et al, J Clin Endocrinol Metab 70:1568, 1990.[12]

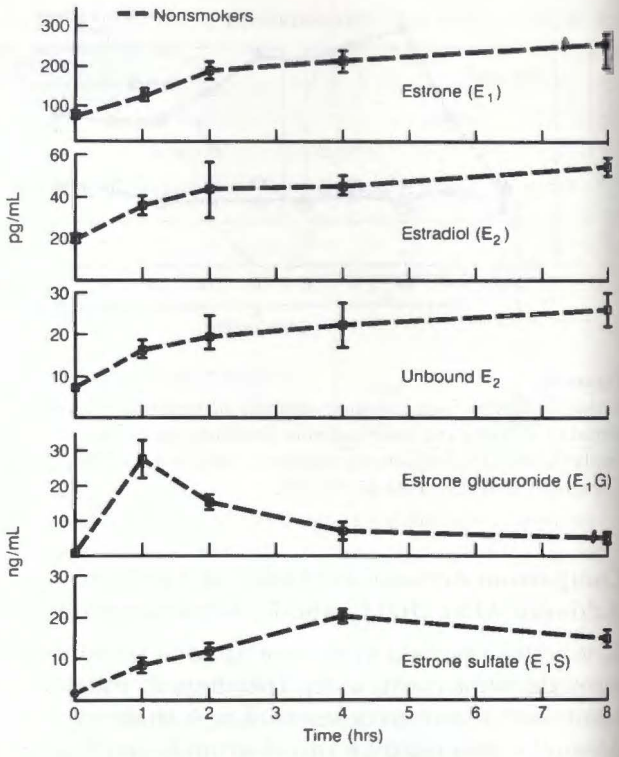

Figure 9
Pharmacokinetics of 1 mg of oral 17 β-estradiol over eight hours in nonsmokers.

(Figure 9). As shown by previous studies with piperazine E_1S (Figure 7),[10] the pharmacokinetics of oral estrogen follow a linear, dose-response relationship. Thus, as depicted in Figure 10, after 2 mg of E_2, the pharmacokinetic profiles are extremely similar. The levels achieved are higher over 12 hours; the E_1 levels at 4 hours are approximately 300 pg/mL and are maintained for the 12 hours of the sampling study. E_2 levels reach approximately 65 pg/mL and also remain elevated for 12 hours.

After the initial increase in E_1G, the levels decrease by four hours, at which time E_1S levels have peaked. With acute dosing, the characteristic serum profile is for the levels to be maintained for at least 12 hours after which a gradual decline occurs, reaching levels still above baseline by 24 hours (data not depicted). It has been surmised from these and other data that 12-hour levels after the oral acute administration of E_2 are representative of the 24-hour pharmacokinetic profile.[7,13] That is not the case in patients receiving estrogen on a chronic basis. Once a steady state occurs, within two to four weeks, the levels of E_2 and E_1 are fairly constant, and the levels seen 24 hours after

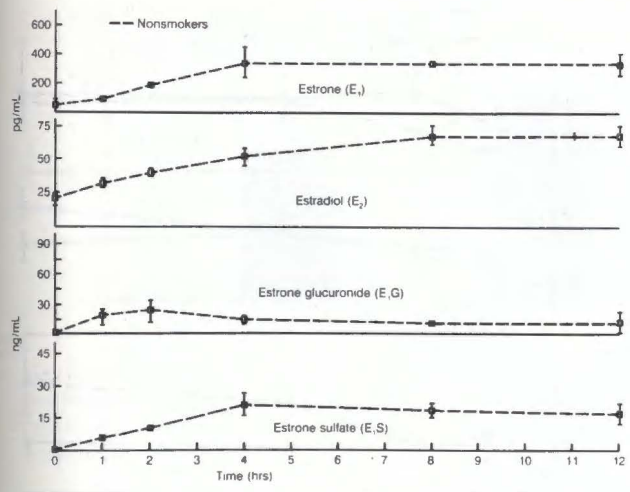

Figure 10
Pharmacokinetics of 2 mg of oral 17 β-estradiol over 12 hours in nonsmokers.

dosing are generally representative of the entire 24-hour profile.[12,14,15] Although the serum profiles are fairly constant, there is more fluctuation with the E_1 levels than with E_2, which remains very constant under steady state conditions although the levels are lower.

What are the levels of serum E_2 and E_1 achieved with multiple dosing of micronized E_2? We measured the levels of E_1 and E_2 after administering 2 mg daily, 2 mg twice daily (a total of 4 mg/d) and 2 mg thrice daily (6 mg/d) (Figures 11 and 12). Those doses of E_2 were taken by women with ovarian failure for purposes of endometrial synchronization for oocyte donation and *in vitro* fertilization. This dosing, therefore, represents both chronic exposure to oral estrogen and

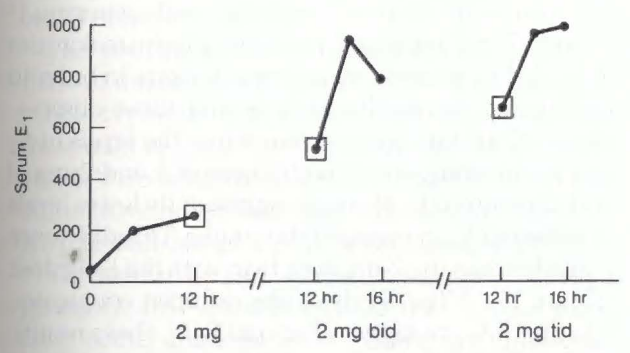

Figure 11
Incremental dosing of 2 mg of oral micronized estradiol: serum estrone (E_1) levels.

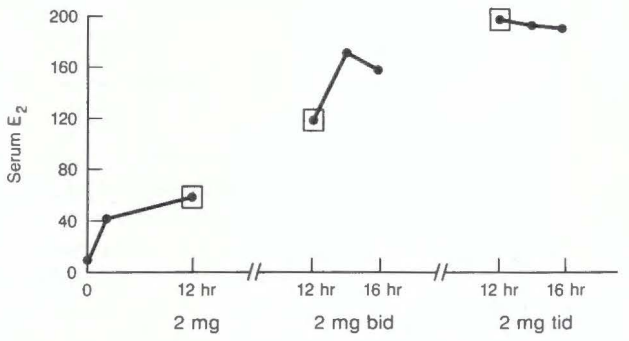

Figure 12
Incremental dosing of 2 mg of oral micronized estradiol (E_2): serum E_2 levels.

bolus increases of 2 mg each time to achieve total daily doses of 4 and 6 mg, respectively.

As shown above, the levels of serum E_1 12 hours after administration are approximately 250 mg/mL. After 4 mg (2 mg twice daily) the 12-hour values (representative of the 24-hour profile) were approximately 560 pg/mL. After 6 mg (2 mg thrice daily) the E_1 level was 700 pg/mL 12 hours after the last 2-mg dose (Figure 12). With each acute dosing of 2 mg taken to achieve the 4- or 6-mg daily dose, an acute increase of 300–400 pg/mL is seen in serum E_1 (Figure 11). It occurs over a four-hour period. The serum E_1 levels then return to basal steady state levels (Figure 12).

A similar pharmacokinetic profile is seen for serum E_2 (Figure 12). With 2 mg of oral micronized E_2 the serum levels of E_2 are 63 pg/mL. A much smaller incremental increase, of only 40 pg/mL, is seen at times with each acute dosing of 2 mg. With the 4-mg dose the serum E_2 levels are approximately 121 pg/mL and with 6 mg, approximately 200 pg/mL (Figures 12 and 13).

For purposes of comparison, the levels of E_1 and E_2 achieved with various doses of conjugated equine estrogen (CEE), E_1S, oral micronized E_2 and E_2V have been tabulated (Table I). The mean serum levels of E_2 and E_1 achieved with E_1S are essentially the same as those after oral micronized E_2, which, in turn, are similar to levels achieved after E_2V. With chronic, incremental dosing, 24-hour levels are representative of the entire day, as discussed above. The 24-hour levels for 2.5 mg of E_1S and 2 mg of micronized E_2 are indicated by an asterisk in Table I and are taken from Colvin's data.[12] The levels achieved after chronic exposure are higher than with acute dosing. With 2 mg of oral micronized E_2 the level of E_1 is 330 pg/mL at 24 hours, which is similar to the 12-hour level after

Table I *Mean Serum Estradiol and Estrone Levels with Conjugated Equine Estrogen, Estrone Sulfate, Micronized Estradiol and Estradiol Valerate*

Dose (mg)	Estradiol (mg)	Estrone (mg)
Estrone sulfate, 0.625	34	125
Estrone sulfate, 1.25	42	220
Estrone sulfate, 2.5[a]	126	356
Micronized estradiol, 1.0	35	190
Micronized estradiol, 2.0	63	300
Micronized estradiol, 2.0[a]	122	330
Estradiol valerate, 1	50	160
Estradiol valerate, 2	60	300

[a]Chronic incremental dosing, 24-hour levels.

acute administration. The E_2 level at 24 hours of chronic ingestion is even higher (122 pg/mL) than the 12-hour level. This finding suggests an accumulated level of E_2 with chronic, incremental dosing. That level may represent a higher total E_2 level from an increase in sex hormone binding globulin (SHBG) but may also be the result of sequestration of E_2 in adipose tissue.

After the ingestion of various doses of conjugated equine estrogen (Table I), the levels of E_1 and E_2 are comparable, on a milligram basis, to the levels of piperazine E_1S and micronized E_2. However, Cee is more potent than E_1S and E_2. In our studies, CEE was three times more potent, on a weight basis, than either E_2S or micronized E_2 in stimulating hepatic globulin production.[16] The reason is that CEE contains other estrogens that are not generally measured but that have considerable biologic potency. Specifically, equilin sulfate, which makes up approximately 25% of the dose of CEE, has been shown to be extremely potent

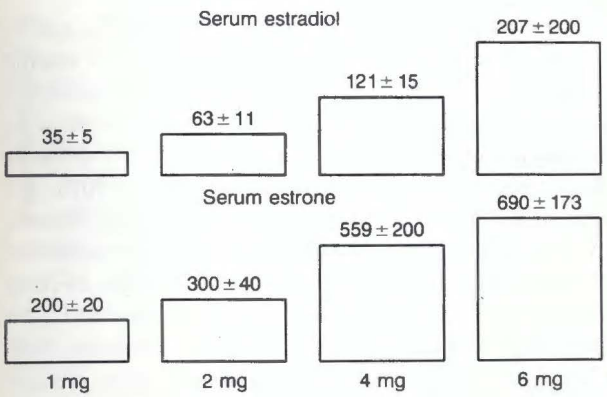

Figure 13
Levels of estrogen with multiple doses of micronized estradiol.

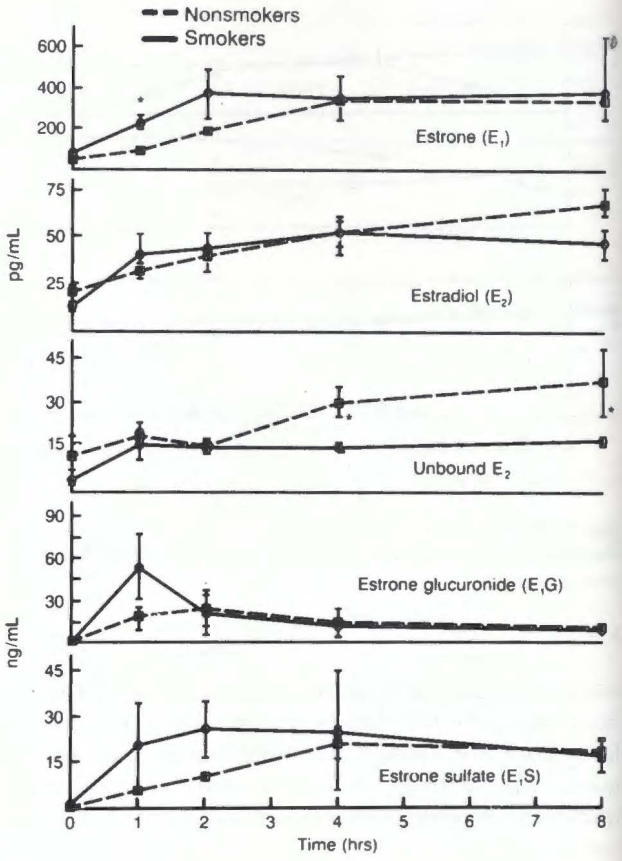

Figure 14
Pharmacokinetics of 2 mg of oral 17 β-estradiol over eight hours in smokers and nonsmokers.

in stimulating hepatic globulins and inducing an increase in HDL cholesterol.[17]

Effects of Smoking on Estrogen Metabolism

It has been suggested that smoking decreases estrogen levels in women receiving oral estrogens.[18] Therefore, we reviewed the acute pharmacokinetics of E_1 and E_2 in smokers and nonsmokers in order to understand the mechanisms behind those observations.[10] Our data suggest that while the levels of E_1 and E_2 are comparable with doses of 1 and 2 mg of oral micronized E_2, there are significantly lower levels of unbound E_2 in women who smoke. This difference is greater than the 2-mg dose than with the 1-mg dose (Figure 14).[10] The levels of the estrogen conjugates, E_1G and E_1S, are higher after oral E_2.[10] These results suggest that with smoking there is enhanced hepatic metabolism of estrogen. This enhanced first passage effect results in lower levels of unbound or free E_2, in

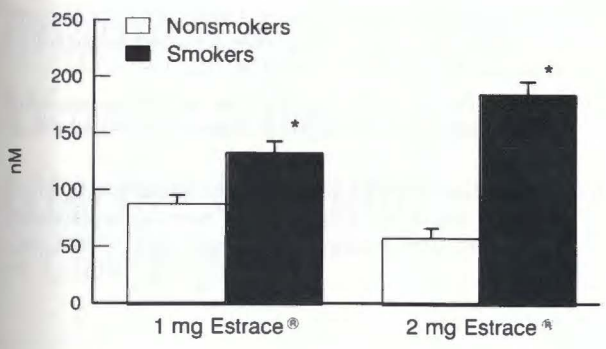

Figure 15
Sex hormone binding globulin after 1 and 2 mg of oral micronized estradiol (Estrace) administered to smokers and nonsmokers.

large part from an increase in SHBG (Figure 15). Thus, smoking accelerates the hepatic metabolism of oral estrogen and also increases SHBG, which reduces the levels of unbound E_2. However, because the effects, at least as studied after acute exposure, are small in moderate smokers, we suggest that there is no reason to recommend a dose alteration in oral estrogen in women who smoke. Indeed, the differences in the levels of E_2 and E_1 were not statistically different. However, with heavy smoking, perhaps a more significant alteration in estrogen metabolism occurs, and higher doses of estrogen may be needed to prevent osteoporosis.

Conclusion

Micronized and conjugated E_2 are absorbed efficiently after oral delivery. E_1 and E_1S are the predominant estrogens in the circulation after the oral administration of either E_2 or E_1. Increases in E_1 glucuronide and E_1S reflect hepatic first passage metabolism after oral delivery.

The pharmacokinetics of oral E_1S are similar to those of micronized E_2 as well as E_2V. The E_2V serum profile is similar to that of oral micronized E_2. From these data one can conclude that oral micronized E_2 and E_2V do not have short serum half-lives after oral administration. In fact, their half-lives are very similar; the half-life of E_1S is approximately 12 hours.

The serum E_1 and serum E_2 values at 12 hours generally are representative of the 24-hour profile after acute administration. There are differences, however, with chronic, incremental regimens of estrogen delivery. It has been shown that 2.5 mg of E_1S is equivalent to 2 mg of oral 17 β-E_2 in terms of the serum E_2 and E_1 levels achieved, suggesting that oral micronized E_2 is perhaps slightly more potent. A chronic, incremental dosing regimen also yields values at 24 hours that are representative of 12-hour values and that are representative of the serum profile of the entire day. With this incremental, chronic regimen, a greater increase in E_2 levels occurs as compared with the levels of E_1. This finding suggests that the levels of E_2 tend to accumulate in the circulation with chronic exposure. An increase in SHBG as well as tissue sequestration may explain this observation.

Smoking enhances hepatic metabolism of oral estrogen, but that phenomenon is clinically evident only with E_2 doses ≥ 2 mg.

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