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# Pharmacokinetics of Oral 17 $\beta$ -Estradiol

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## Introduction

Reviewing the pharmacokinetics of oral 17 $\beta$ -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,<sup>1</sup> 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.<sup>2</sup> 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 ( $E_1S$ ).<sup>3</sup> 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 metabolism into  $E_1$  or  $E_1S$ . Although sulfates of  $E_2$  and estriol also exist, the levels of those compounds are much lower.<sup>4</sup>

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

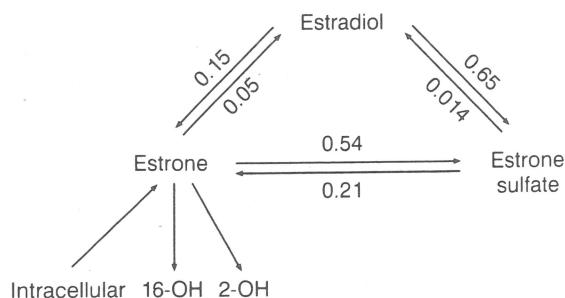
The pharmacokinetics of oral 17 $\beta$ -estradiol ( $E_2$ ) were evaluated: only a limited amount of information is available on the subject. Because of the first passage hepatic effect, the blood levels of estrone ( $E_1$ ) are greater than those of  $E_2$ ; similar profiles exist for oral  $E_1$  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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**Figure 1**  
Estradiol metabolism.

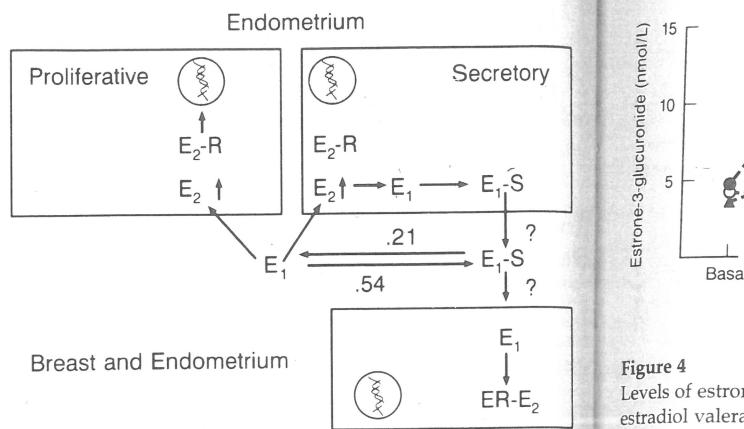
the predominant estrogen in the circulation. However, when E<sub>1</sub> is taken up by cells, it is converted primarily to E<sub>2</sub>. It has been shown that the principal intranuclear estrogen is E<sub>2</sub>.<sup>5</sup> In the secretory endometrium, under the effects of progesterone, E<sub>2</sub> is converted through 17 $\beta$ -E<sub>2</sub> dehydrogenase to E<sub>1</sub> and then is sulfurylated to E<sub>1</sub>S. This step essentially deactivates the potency of E<sub>2</sub> in the cell, and E<sub>1</sub> may exit into the circulation.

As discussed above, E<sub>1</sub> and E<sub>1</sub>S may be interconverted in blood. Although not completely established, E<sub>1</sub>S also may be taken up by cells, such as in the breast, where sulfatase activity is able to liberate E<sub>1</sub> and E<sub>2</sub> in turn (Figure 2).<sup>6,7</sup>

#### Oral and Systemic Routes of Administration

E<sub>1</sub> 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<sub>2</sub> is ingested, the liver actively deactivates E<sub>2</sub> by its metabolism into E<sub>1</sub> and E<sub>1</sub> conjugates. Some estrogen does enter the systemic circulation as E<sub>2</sub>. However, E<sub>1</sub> is the predominant estrogen after oral E<sub>2</sub> administration, and the metabolites of E<sub>1</sub>—E<sub>1</sub>S and, more specifically, E<sub>1</sub> glucuronide (E<sub>1</sub>G)—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<sub>2</sub> administered systemically is converted to E<sub>1</sub> 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.<sup>8</sup> That E<sub>1</sub>G is an important marker of the first passage effect of oral administration is illustrated in Figure 4. Within three



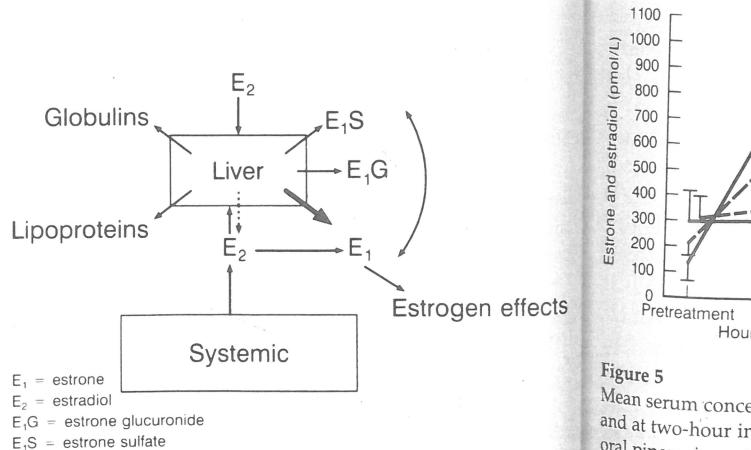
**Figure 2**  
Estrone (E<sub>1</sub>), estradiol (E<sub>2</sub>) and estrone sulfate (E<sub>1</sub>S) interaction in tissues.

**Figure 4**  
Levels of estrone, estradiol valerate, implantation of Contemp Obstet

#### Comparison Achieved After

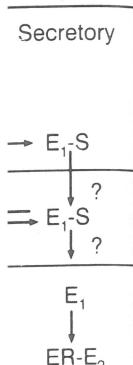
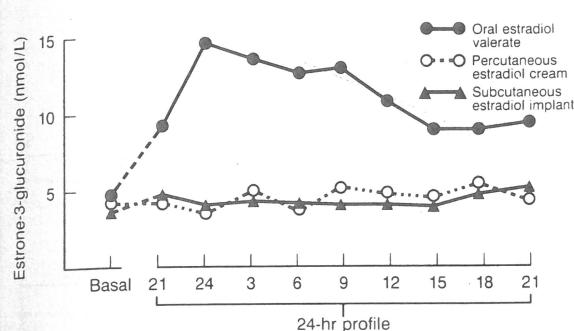
hours there is approximately a threefold increase in serum E<sub>1</sub>G with oral administration of E<sub>2</sub>. V. That does not occur, however, with the systemic forms, in which serum E<sub>1</sub>G levels remain low.<sup>9</sup>

Once in the circulation, both E<sub>1</sub> and E<sub>2</sub> will express estrogen-related effects on the brain, cardiovascular system and bone. That is a reflection of the levels of E<sub>1</sub> and E<sub>2</sub> achieved and is independent of whether the estrogen is derived from oral or systemic administration. However, it is well known that E<sub>2</sub> is more potent than E<sub>1</sub>, and it can be estimated that the levels of E<sub>1</sub> in blood required to equal the biologic effects of E<sub>2</sub> are at least threefold greater.



**Figure 3**  
Oral versus systemic estradiol delivery.

**Figure 5**  
Mean serum concentrations of estrone and estradiol at pretreatment and at two-hour intervals in oral piperazine ester-treated postmenopausal women (1:140, 1978).<sup>10</sup>

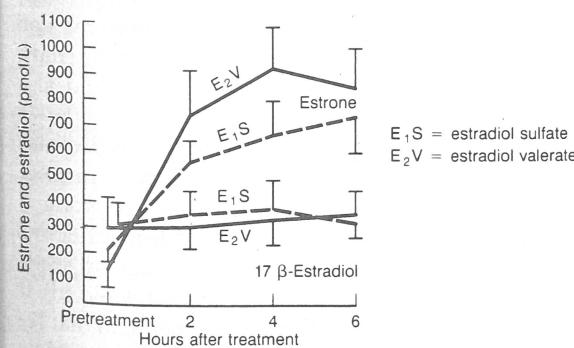
E<sub>1</sub>-S interaction

**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.<sup>9</sup>

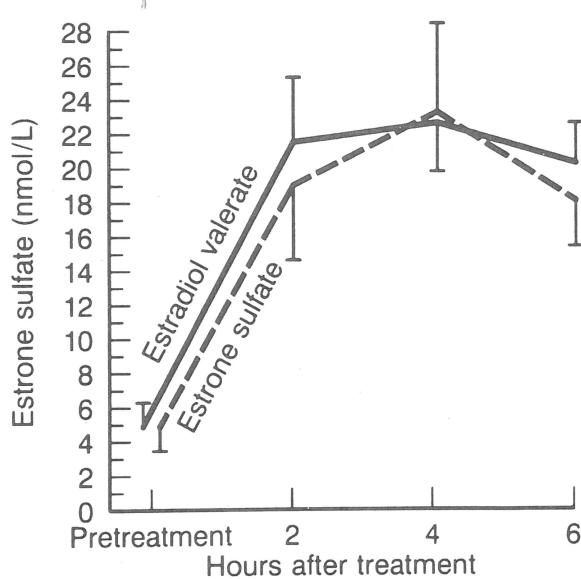
### Comparison Between the Levels of Estrogen Achieved After Oral E<sub>2</sub> and E<sub>1</sub> Administration

E<sub>2</sub> is better absorbed in its conjugated or micronized form; the same is true of E<sub>1</sub>. Therefore, E<sub>1</sub> usually is administered as the conjugate, E<sub>1</sub>S. A study by Anderson<sup>10</sup> compared the levels of serum E<sub>1</sub> and E<sub>2</sub> after the administration of 1.5 mg of oral piperazine E<sub>1</sub>S and 2 mg of E<sub>2</sub>V. The serum levels of E<sub>2</sub> achieved were nearly identical (Figure 5). Although the pharmacokinetics were similar, E<sub>2</sub>V administered at a higher dose, 2 mg as compared with 1.5 mg of E<sub>1</sub>S, resulted in levels of E<sub>1</sub> that were slightly higher. Serum E<sub>1</sub>S levels after E<sub>2</sub>V and E<sub>1</sub>S were again almost superimposable (Figure 6). Peak levels of E<sub>2</sub>, E<sub>1</sub> and

old increase in E<sub>2</sub>V. That does not mean, in which E<sub>2</sub> will express cardiovascular effects. The levels of E<sub>1</sub> depend on whether the oral administration is more potent than the levels of E<sub>1</sub> in the effects of E<sub>2</sub> are at



**Figure 5**  
Mean serum concentrations of estrone and 17  $\beta$ -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.<sup>10</sup>

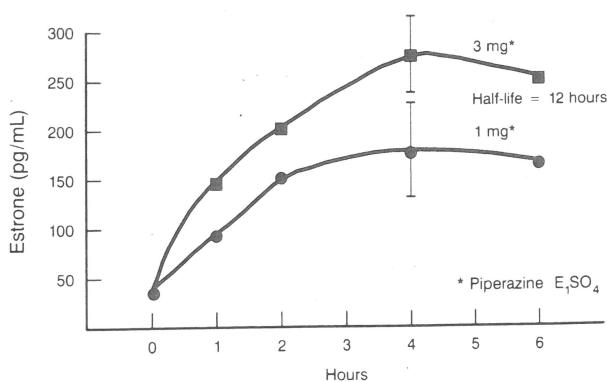


**Figure 6**  
Comparison of estrone sulfate levels after estradiol valerate and estrone sulfate administration. From Anderson ABM et al, *Br Med J* 1:140, 1978.<sup>10</sup>

E<sub>1</sub>S occurred at approximately four hours with each preparation.

The administration of 1 and 3 mg of piperazine E<sub>1</sub>S also suggests a linear dose-response relationship in the pharmacokinetics of E<sub>1</sub>S administration (Figure 7). Serum levels that peak at four hours were seen in one study<sup>10</sup> to be maintained for many hours. The data suggest that the half-life of E<sub>1</sub>S is approximately 12 hours.<sup>10</sup> Other studies that have compared the pharmacokinetics of E<sub>2</sub>V and E<sub>1</sub>S also have suggested similar half-life characteristics.<sup>11</sup> The studies to date, therefore, suggest that in terms of E<sub>2</sub> and E<sub>1</sub> 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<sub>2</sub> and E<sub>1</sub> administered orally remains unclear. A recent study by Colvin et al<sup>12</sup> suggested that with an incremental oral regimen after the highest dose of estrogen, which was either 2.5 mg of E<sub>1</sub>S (Ogen) or 2 mg of oral micronized E<sub>2</sub> (Estrace), there was a greater increase in HDL cholesterol after the E<sub>2</sub> was administered. While the two doses achieved the same serum concentrations of E<sub>1</sub> and E<sub>2</sub>, there was a greater increase in HDL cholesterol and a greater reduction in low density lipoprotein cholesterol with

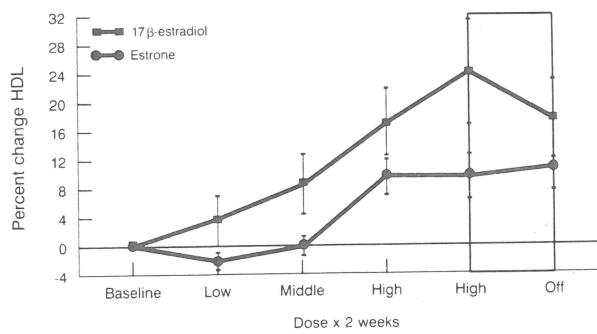


**Figure 7**  
Levels of estrone after two doses of estrone sulfate. From Anderson ABM et al, Br Med J 1:140, 1978.<sup>10</sup>

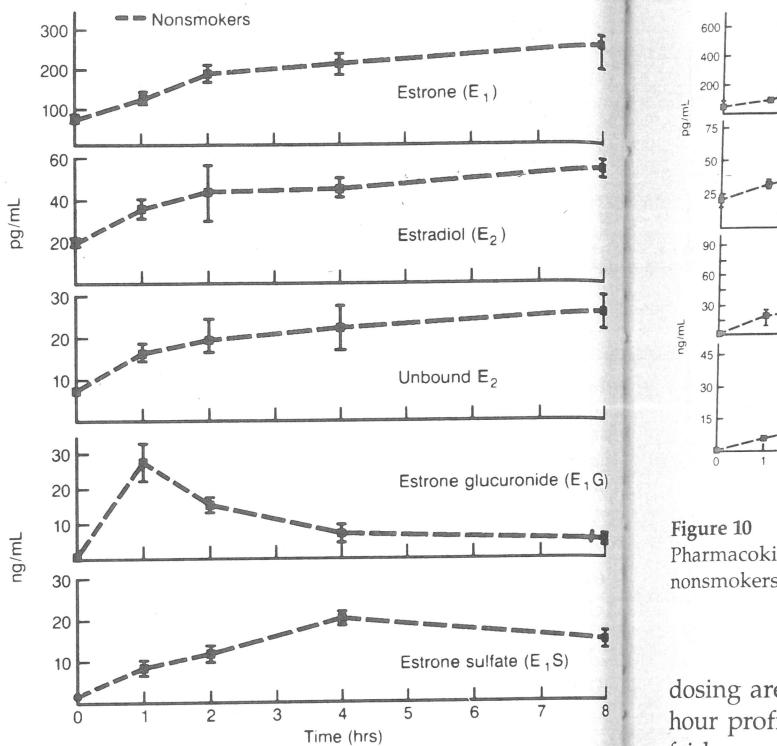
$E_2$  than with piperazine  $E_1S$  (Figure 8). These results suggest that with oral administration there may be some subtle biologic differences related to inherent differences in the potency of  $E_2$  and  $E_1$ . Clearly, more work is needed in this area.

#### Pharmacokinetics of Oral $17\beta$ - $E_2$

With oral administration of 1 mg of  $\beta$ - $E_2$ , serum levels of  $E_1$  and  $E_2$  increase rapidly during the first four to eight hours after ingestion.<sup>13</sup> 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



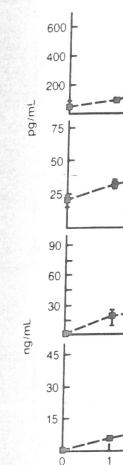
**Figure 8**  
Percentage change in high density lipoprotein cholesterol from baseline concentrations to low, middle and high doses of 17 $\beta$ -estradiol and estrone sulfate. From Colvin P et al, J Clin Endocrinol Metab 70:1568, 1990.<sup>12</sup>



**Figure 9**  
Pharmacokinetics of 1 mg of oral 17 $\beta$ -estradiol over eight hours in nonsmokers.

(Figure 9). As shown by previous studies with piperazine  $E_1S$  (Figure 7),<sup>10</sup> 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.

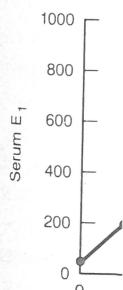
After the initial increase in  $E_1G$ , the levels decrease by four hours, at which time  $E_1S$  levels have peaked. With acute dosing, the characteristic serum profile is for the levels to be maintained for at least 12 hours, after which a gradual decline occurs, reaching levels still above baseline 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.<sup>7,13</sup> 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



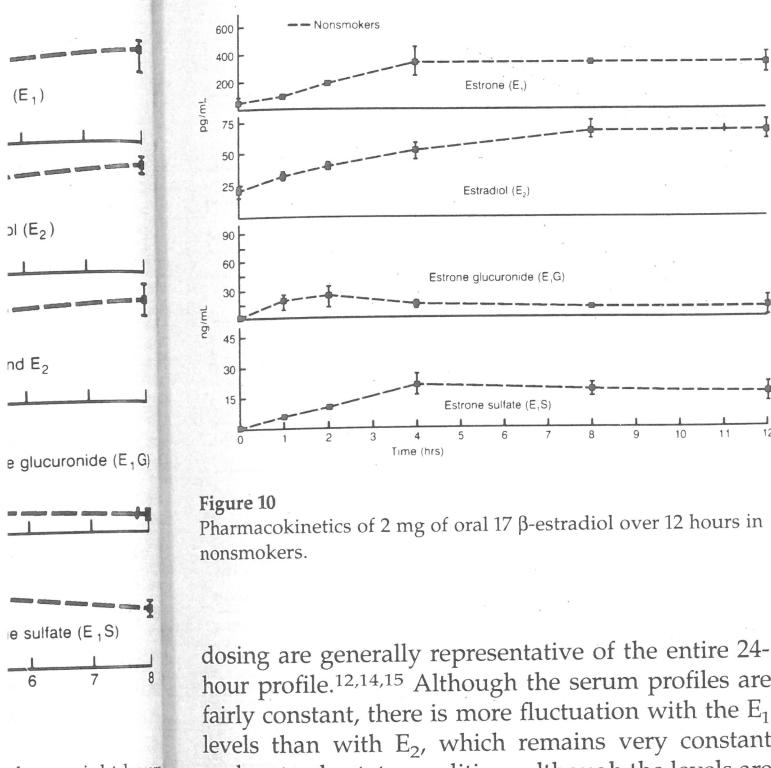
**Figure 10**  
Pharmacokinetics in nonsmokers

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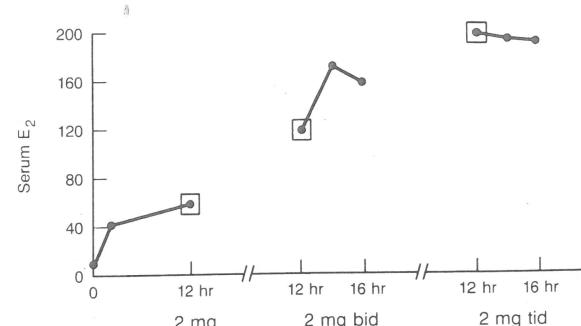
**Figure 11**  
Incremental c estrone ( $E_1$ ) le



**Figure 10**  
Pharmacokinetics of 2 mg of oral 17 $\beta$ -estradiol over 12 hours in nonsmokers.

dosing are generally representative of the entire 24-hour profile.<sup>12,14,15</sup> Although the serum profiles are fairly constant, there is more fluctuation with the E<sub>1</sub> levels than with E<sub>2</sub>, which remains very constant under steady state conditions although the levels are lower.

What are the levels of serum E<sub>2</sub> and E<sub>1</sub> achieved with multiple dosing of micronized E<sub>2</sub>? We measured the levels of E<sub>1</sub> and E<sub>2</sub> 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<sub>2</sub> 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



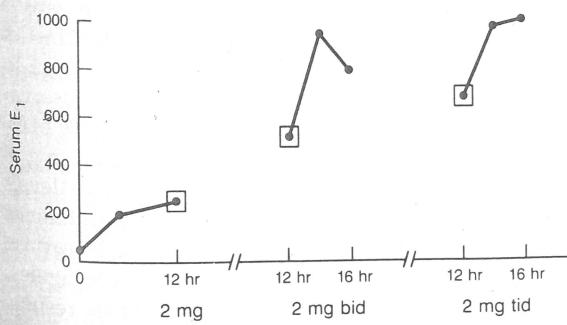
**Figure 12**  
Incremental dosing of 2 mg of oral micronized estradiol (E<sub>2</sub>): serum E<sub>2</sub> levels.

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<sub>1</sub> 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<sub>1</sub> 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<sub>1</sub> (Figure 11). It occurs over a four-hour period. The serum E<sub>1</sub> levels then return to basal steady state levels (Figure 12).

A similar pharmacokinetic profile is seen for serum E<sub>2</sub> (Figure 12). With 2 mg of oral micronized E<sub>2</sub> the serum levels of E<sub>2</sub> 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<sub>2</sub> 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<sub>1</sub> and E<sub>2</sub> achieved with various doses of conjugated equine estrogen (CEE), E<sub>1</sub>S, oral micronized E<sub>2</sub> and E<sub>2</sub>V have been tabulated (Table I). The mean serum levels of E<sub>2</sub> and E<sub>1</sub> achieved with E<sub>1</sub>S are essentially the same as those after oral micronized E<sub>2</sub>, which, in turn, are similar to levels achieved after E<sub>2</sub>V. 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<sub>1</sub>S and 2 mg of micronized E<sub>2</sub> are indicated by an asterisk in Table I and are taken from Colvin's data.<sup>12</sup> The levels achieved after chronic exposure are higher than with acute dosing. With 2 mg of oral micronized E<sub>2</sub> the level of E<sub>1</sub> is 330 pg/mL at 24 hours, which is similar to the 12-hour level after



**Figure 11**  
Incremental dosing of 2 mg of oral micronized estradiol: serum estrone (E<sub>1</sub>) levels.

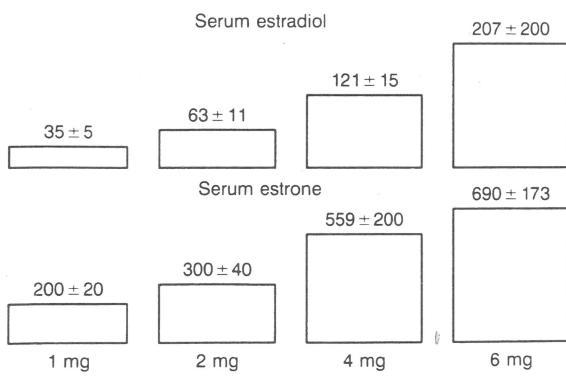
**Table I** Mean Serum Estradiol and Estrone Levels with Conjugated Equine Estrogen, Estrone Sulfate, Micronized Estradiol and Estradiol Valerate

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

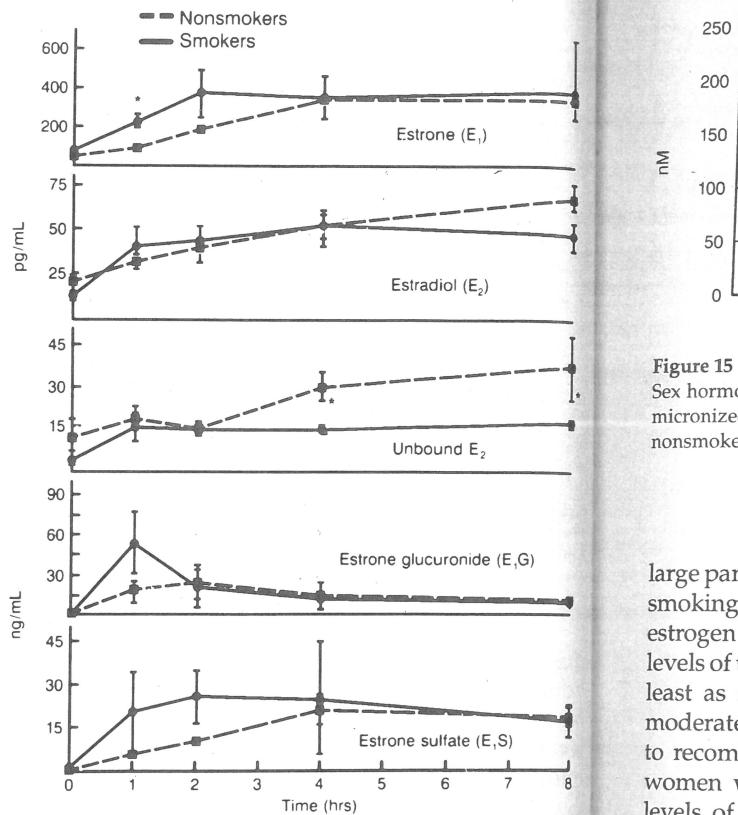
<sup>a</sup>Chronic incremental dosing, 24-hour levels.

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.<sup>16</sup> 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 $\beta$ -estradiol over eight hours in smokers and nonsmokers.

in stimulating hepatic globulins and inducing an increase in HDL cholesterol.<sup>17</sup>

#### Effects of Smoking on Estrogen Metabolism

It has been suggested that smoking decreases estrogen levels in women receiving oral estrogens.<sup>18</sup> 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.<sup>10</sup> 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).<sup>10</sup> The levels of the estrogen conjugates,  $E_1G$  and  $E_1S$ , are higher after oral  $E_2$ .<sup>10</sup> 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

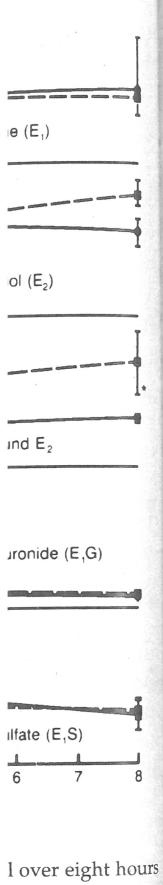
large part due to smoking. The sex hormone levels of nonsmokers are at least as high as those of moderate to heavy smokers. The levels of  $E_2$  are higher in nonsmokers.

#### Conclusion

Micronized estradiol is a potent and effective agent for the treatment of menopausal symptoms. It is well absorbed orally and has a long half-life.

The pharmacokinetic profile of micronized estradiol is similar to that of oral estradiol. These data support the use of micronized estradiol in the treatment of menopausal symptoms.

The series of studies presented here generally support the findings of previous studies. After acute administration, however, the pharmacokinetic profile of micronized estradiol is equivalent to that of oral estradiol.



**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<sub>2</sub>. 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<sub>2</sub> and E<sub>1</sub> 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<sub>2</sub> are absorbed efficiently after oral delivery. E<sub>1</sub> and E<sub>1</sub>S are the predominant estrogens in the circulation after the oral administration of either E<sub>2</sub> or E<sub>1</sub>. Increases in E<sub>1</sub> glucuronide and E<sub>1</sub>S reflect hepatic first passage metabolism after oral delivery.

The pharmacokinetics of oral E<sub>1</sub>S are similar to those of micronized E<sub>2</sub> as well as E<sub>2</sub>V. The E<sub>2</sub>V serum profile is similar to that of oral micronized E<sub>2</sub>. From these data one can conclude that oral micronized E<sub>2</sub> and E<sub>2</sub>V do not have short serum half-lives after oral administration. In fact, their half-lives are very similar; the half-life of E<sub>1</sub>S is approximately 12 hours.

The serum E<sub>1</sub> and serum E<sub>2</sub> 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<sub>1</sub>S is equivalent to 2 mg of oral 17 $\beta$ -E<sub>2</sub> in terms of the

serum E<sub>2</sub> and E<sub>1</sub> levels achieved, suggesting that oral micronized E<sub>2</sub> 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<sub>2</sub> levels occurs as compared with the levels of E<sub>1</sub>. This finding suggests that the levels of E<sub>2</sub> 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<sub>2</sub> doses  $\geq 2$  mg.

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