Single-Dose Pharmacokinetics of Sublingual Versus Oral Administration of Micronized 17β-Estradiol

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Objective: **To investigate the pharmacokinetic profiles of different doses of micronized 17β-estradiol administered by oral or sublingual routes.**

Methods: **Single doses of micronized 17β-estradiol were administered orally (1 mg, 0.5 mg) or sublingually (1 mg, 0.5 mg, 0.25 mg) to six postmenopausal women in a randomized clinical trial. We calculated pharmacokinetic parameters for estradiol (E2) and estrone (E1) of maximum serum concentration, time to maximum serum concentration, terminal half-life, area under the concentration curve, and oral clearance. Serum levels of E1 sulfate also were compared at 4, 12, and 24 hours after dosing.**

Results: **Sublingual administration resulted in rapid absorption with significantly higher E2 levels than did comparable oral dosing. Estrone levels did not vary with route of administration but correlated with the dosage administered. Estrone sulfate levels correlated with the dosage administered and also tended to be higher with sublingual administration. Sublingual administration resulted in a significantly lower E1 to E2 ratio during the 24 hours than did oral administration.**

Conclusion: **Sublingual administration of micronized 17β-estradiol results in a rapid, burst-like absorption into the systemic circulation, yielding high E2 levels that fall rapidly over the first 6 hours.** *(Obstet Gynecol 1997;89:340–5.*

The route of administration affects the metabolism of estradiol (E2) administered for hormone replacement therapy. Orally administered micronized 17β-estradiol (Estrace; Bristol-Myers Squibb, Princeton, NJ) is metabolized initially by oxidation at the C17 position to estrone (E1) by the gastrointestinal mucosa and liver, resulting in circulating ratios of E1 to E2 of approximately 5:1.[1,2] Non-oral administration of E2, such as transdermal, vaginal, or sublingual administration, bypasses this initial metabolism by the gastrointestinal tract and results in circulating ratios of E1 to E2 of approximately 1:1–2.[3,4] Of the non-oral routes of therapy, sublingual administration has received the least amount of attention in the literature despite its possible advantages. Sublingual administration is more convenient than vaginal administration and does not have the potential complication of skin irritation sometimes seen with transdermal administration.

Investigators are recognizing that the route, dose, and type of estrogen administered result in different physiologic responses. Dose-dependent effects of estrogen have been shown in relation to bone resorption,[5] whereas the route of administration and type of estrogen preparation are known to affect liver protein production differentially.[6] Because E2 is a more potent estrogen than E1, replacement therapy resulting in higher circulating E2 levels may have greater physiologic action than other circulating estrogens. Theoretically, increased estrogen action might be beneficial in some clinical situations, eg, in women with osteoporosis or prone to vasospastic phenomena such as angina or migraine headaches. The purpose of this study was to evaluate the circulating levels of E2, E1, and E1 sulfate resulting from differing doses of micronized 17β-estradiol administered sublingually versus orally.

Materials and Methods

Seven postmenopausal women were recruited by advertisement for this randomized, non-blinded clinical

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trial to compare the single-dose pharmacokinetics of sublingual versus oral dosing of micronized 17β-estradiol (Estrace). One subject was removed from the study (poor venous access made it difficult to obtain blood samples), leaving six women for analysis. This study was approved by the Greenville Hospital System Institutional Review Committee, and each woman signed an informed consent form. Women ranged in age from 54 to 65 years with a mean ± standard deviation of 57.5 ± 4.23 years. Five of the six women had never received estrogen replacement therapy, and one subject had discontinued estrogen therapy 8 weeks before the study. Body mass index of the six subjects was 29.7 ± 6.06 kg/m^2, with a weight range of 57–120 kg. All women were nonsmokers, and none reported an alcohol intake of greater than one alcoholic drink per week. Other exclusion criteria included renal or hepatic disease, use of drugs known to alter estrogen metabolism, and history of an estrogen-dependent malignancy. Prescribed medications taken by the subjects included guanfacine, etodolac, fluoxetine, acyclovir, levothyroxine, and trazodone. The one subject taking levothyroxine had a normal TSH level before initiation of the study.

After an overnight fast, each subject randomly received one of the following doses and routes of administration of micronized 17β-estradiol: 1 mg sublingual, 0.5 mg sublingual, 0.25 mg sublingual, 1 mg oral, or 0.5 mg oral. At initial dosing, the subjects were assigned randomly to the five doses. Each subsequent dosage was assigned using a completely randomized block design. Breeze/STAT software (Version 1.1; GRG Associates, Indianapolis, IN) was used to generate initial randomization. Each subject then received each of the other dosages and routes randomly at weekly intervals until the study was completed. After drug administration the subject remained fasting for 2 hours. Blood was drawn via a percutaneous intravenous catheter at hours 0, 1, 2, 3, 4, 6, 8, 12, 18, and 24 after dosing. Serum was stored at −80C until assayed for E2 and E1. Estrone sulfate was measured at 0, 4, 12, and 24 hours. Values obtained at 0 hour before dosing were subtracted from subsequent post-dosing values before calculation of pharmacokinetic parameters. Each subject completed all five different treatment regimens. We excluded E2 data from one subject obtained during the planned 0.5-mg oral treatment because the drug was mistakenly administered sublingually.

To distinguish times to maximum serum concentration, we compared results from sublingual administration to those from oral administration using Wilcoxon signed-rank test with an α of .05. Data for the other pharmacokinetic parameters were analyzed using repeated measures analysis of variance. Significance levels for overall tests were based on the Greenhouse-Geisser[7] adjusted tests provided by SAS software (SAS Institute, Inc., Cary, NC). The Greenhouse-Geisser method is used to adjust the P value of the test statistic to account for the fact that the variances of the treatment differences may not be homogeneous. Multiple comparisons were evaluated using an α of .01, which was obtained by dividing the overall α (.1) by the number of possible pair-wise comparisons (10). We calculated power analyses for the pharmacokinetic parameters of E2 and E1 and for the comparisons of E1 sulfate serum levels. For E2, the power to determine differences in maximum serum concentration (Cmax), terminal half-life, area under the serum concentration versus time curve (AUC0–24h), and oral clearance was .99, .75, .99, and .90, respectively; for E1 the corresponding values were .94, .65, .98, and .46. The power to determine differences in the serum levels of E1 sulfate at 4, 12, and 24 hours was .98, .87, and .97, respectively.

Pharmacokinetic parameters for both E2 and E1 were calculated using noncompartmental analysis. We determined the Cmax and the time to the maximum serum concentration (Tmax) by observation of the serum concentration–time data. Terminal half-life and elimination rate constant (K_e) were determined by analysis of two points on the terminal portion of the log concentration–time profile observed to be on a straight line. Area under the serum concentration versus time curve was calculated by the trapezoidal rule. Apparent oral clearance was calculated using CL/F = dose/AUC, where CL is oral clearance and F is oral bioavailability, which was unknown in this study and assumed to be 1.

We measured E2, E1, and E1 sulfate in serum by specific radioimmunoassays (RIA). Estradiol was quantified by ethyl acetate:hexane extraction and use of a double antibody RIA kit (Pantex, Santa Monica, CA). We used modification of the procedure recommended by the manufacturer.[3] Estrone was measured directly in serum using a double antibody RIA kit from Diagnostic Systems Laboratory (Webster, TX). Quantification of E1 sulfate was performed by ethyl acetate:hexane extraction of unconjugated steroids, followed by hydrolysis of the sulfate-conjugated compounds in the aqueous phase and RIA for E1.[8] Sensitivity of the assays for E2, E1, and E1 sulfate was 8, 15, and 160 pg/mL, respectively. Intra-assay coefficients of variation were 9.2, 7.4, and 7.5%, and the interassay coefficients of variation were 12.5, 7.7, and 11% for E2, E1, and E1 sulfate, respectively.

Results

Table 1 shows the pharmacokinetic parameters derived from serum E2 and E1 concentrations. With respect to

Table 1. Pharmacokinetic Parameters for Serum Concentrations of Estradiol and Estrone

Parameter	Dosage	Estradiol Mean ± SD	Estradiol P*	Estrone Mean ± SD	Estrone P*
Cmax (pg/mL)	1.0 mg SL	451 ± 162	.001†	164 ± 86.7	.003†
	0.5 mg SL	245 ± 115		85.3 ± 23.6	
	0.25 mg SL	294 ± 131		59.5 ± 25.9	
	1.0 mg PO	34.0 ± 20.4		169 ± 60.4	
	0.5 mg PO	24.8 ± 17.5		81.8 ± 39.4	
t1/2 (hr)	1.0 mg SL	18.0 ± 2.5	.510	12.6 ± 4.0	.160
	0.5 mg SL	14.2 ± 9.1		13.9 ± 7.3	
	0.25 mg SL	8.3 ± 2.9		7.3 ± 3.9	
	1.0 mg PO	20.1 ± 14.2		12.3 ± 5.5	
	0.5 mg PO	14.2 ± 8.0		14.2 ± 1.1	
AUC0–24h (pg/mL · hr)	1.0 mg SL	2109 ± 1031	.034†	3506 ± 1923	.018†
	0.5 mg SL	970 ± 440		1364 ± 760	
	0.25 mg SL	825 ± 401		570 ± 183	
	1.0 mg PO	823 ± 636		2923 ± 1978	
	0.5 mg PO	403 ± 142		1288 ± 466	
CL (1/hr · kg)	1.0 mg SL	7.6 ± 4.5	.220	4.1 ± 1.4	.230
	0.5 mg SL	8.3 ± 4.8		5.6 ± 2.2	
	0.25 mg SL	4.7 ± 2.5		6.2 ± 2.9	
	1.0 mg PO	27.2 ± 26.4		5.3 ± 2.0	
	0.5 mg PO	18.1 ± 12.3		4.5 ± 1.3	

SD = standard deviation; Cmax = maximum serum concentration; SL = sublingual; PO = oral; t1/2 = terminal half-life; AUC = area under the serum concentration versus time curve; CL = oral clearance.

* *P* values from repeated measures analysis of variance.

† See results in text for significant differences within groups.

the pharmacokinetic parameters of E2, significant differences among the treatments were found in the Tmax, Cmax, and AUC0–24h. With sublingual administration, the time to maximum E2 concentration was 1 hour or less for all three doses. The Tmax could have been less than 1 hour, because this was the first time point analyzed. With oral administration, the Tmax was 6.5 ± 8.6 hours for the 1-mg dose and 7.6 ± 6.2 hours for the .5-mg dose. The Tmax was significantly different between the sublingual and oral routes of administration at all doses ($P = .04$).

All sublingual doses (1 mg, 0.5 mg, 0.25 mg) gave significantly higher peak E2 levels of Cmax than did either of the oral doses. For example, a 1-mg sublingual dose yielded a Cmax 13-fold greater than did the corresponding oral dose, whereas a 0.5-mg sublingual dose resulted in a Cmax tenfold greater than did the corresponding oral dose. In addition, the Cmax for the 1-mg sublingual dosing was significantly higher (1.8-fold) than the Cmax for the 0.5-mg sublingual dosing. There was no difference in the Cmax between the oral doses of 1 mg and 0.5 mg or between the sublingual doses of 0.5 mg and 0.25 mg.

The 1-mg sublingual dosing resulted in significantly higher AUC0–24h levels than did either the 1-mg oral (2.6-fold) or the 0.5-mg oral (5.20-fold) dosing. When only the sublingual route of administration is considered, the 1-mg dose yielded a significant twofold higher AUC0–24h than did the 0.5 mg dose and a 2.5-fold higher AUC0–24h than did the 0.25-mg dose. There were no differences in AUC0–24h between the oral doses, between the 0.5-mg sublingual and either of the oral doses, or between the 0.25-mg sublingual and either of the oral doses.

Evaluation of the pharmacokinetic data for the serum E1 levels revealed significant differences in the Cmax and in the AUC0–24h. In contrast to the data for E2, there was no difference in the Tmax according to dose or route of administration. The Tmax for the 1-mg, 0.5-mg, and 0.25-mg sublingual doses was 6.2 ± 3.8, 2.5 ± 2.8, and 2.5 ± 2.1 hours, respectively. The respective values for the 1-mg and 0.5-mg oral doses were 3.7 ± 1.2 and 5.0 ± 2.4 hours. The 1-mg sublingual dose resulted in a significantly greater Tmax for E1 than did the 0.5-mg sublingual dose ($P = .04$) or the .25-mg sublingual dose ($P = .03$). There was also a significant difference in the Tmax between the 0.25-mg sublingual dose and the 0.5-mg oral dose ($P = .05$).

Regarding the regimen's effect on Cmax, 1-mg oral dosing yielded a significantly higher peak E1 level (twofold) than did 0.5-mg oral dosing, a twofold higher level than did 0.5-mg sublingual dosing, and a 2.8-fold higher level than did 0.25-mg sublingual dosing. One-mg sublingual dosing resulted in higher peak E1 levels than did either 0.25-mg sublingual (2.7-fold) or 0.5-mg oral (twofold) dosing, with α values that approached significance ($P = .017$).

The results for AUC0–24h showed a significantly higher level (2.5-fold) with 1-mg sublingual dosing when compared to 0.5-mg sublingual dosing and a sixfold higher level than with 0.25-mg sublingual dosing. In addition, 0.5-mg oral dosing resulted in a 2.4-fold higher AUC0–24h for E1 than did 0.25-mg sublingual dosing. Figures 1 and 2 illustrate the serum concentration versus time curves for E2 and E1, respectively. There was a rapid decrease in E2 levels within the first 6 hours after sublingual dosing.

Figure 3 shows the ratio of estrone to estradiol (E1/E2) for the oral compared to the sublingual route of administration. For this analysis, dosages for each route were combined. Oral dosing yielded a significantly higher E1/E2 at times 2, 3, 6, 8, and 18 hours after administration compared to that of sublingual dosing. With sublingual administration, the E1/E2 remained less than 1 until 2 hours after dosing; it then varied from 2 to 3 for the remainder of the 24 hours.

Table 2 illustrates the E1 sulfate data, which were analyzed at 4, 12, and 24 hours. Of the three time points,

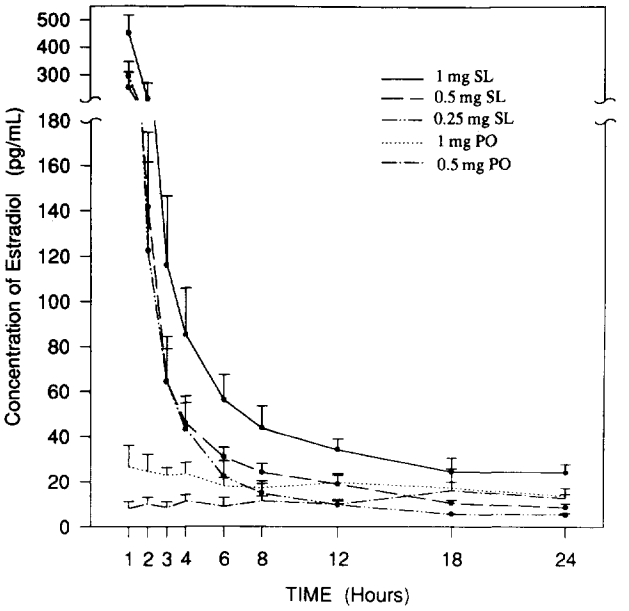

Figure 1. Serum concentrations of estradiol (mean ± standard deviation) during a 24-hour period after single oral (PO) or sublingual (SL) dosing with micronized 17β-estradiol.

statistical differences within groups were found at 4 hours and at 12 hours. In multiple comparisons, the 0.5-mg sublingual dose yielded higher levels of E1 sulfate than did the 0.25-mg sublingual dose, and the 1-mg oral dose resulted in higher levels than did the 0.25-mg sublingual dose at both time points.

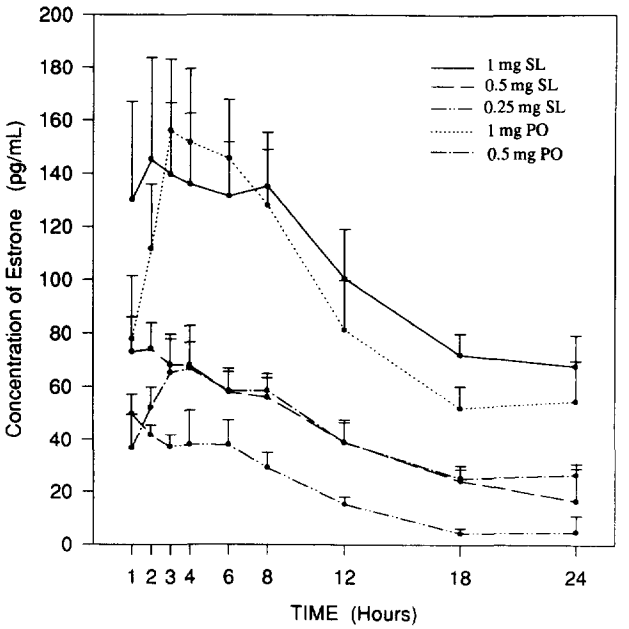

Figure 2. Serum concentrations of estrone (mean ± standard deviation) during a 24-hour period after single oral (PO) or sublingual (SL) dosing with micronized 17β-estradiol.

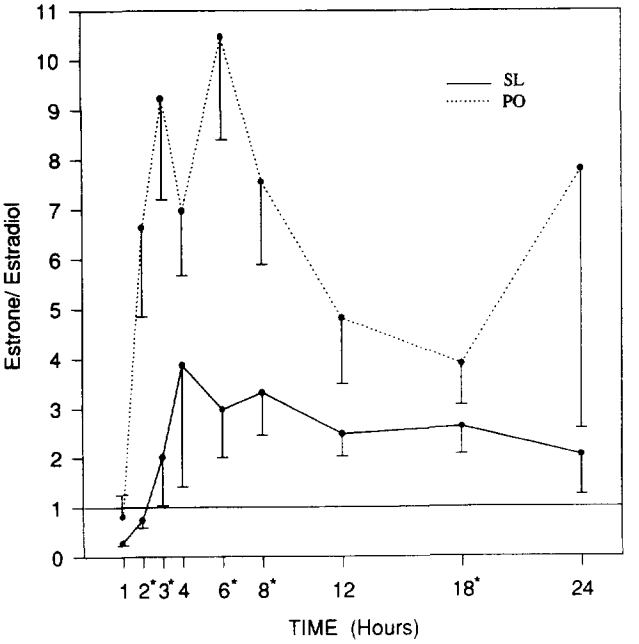

Figure 3. Ratio of estrone to estradiol after either oral (PO) (dotted line) or sublingual (SL) (solid line) administration of micronized 17β-estradiol. For simplification, dosages for each route of administration were combined. * indicates a significant difference between oral and sublingual administration ($P \leq .05$).

Subjects tolerated sublingual administration well. Subjects reported no taste or other sensation, and the tablet dissolved quickly, within approximately 1–2 minutes.

Table 2. Mean Serum Concentrations of Estrone Sulfate

Time	Dosage	Mean ± SD (ng/mL)	P*
4 hours	1.0 mg SL	11.8 ± 9.2	.058†
	0.5 mg SL	6.7 ± 2.6	
	0.25 mg SL	2.3 ± 1.5	
	1.0 mg PO	14.2 ± 5.6	
	0.5 mg PO	4.4 ± 3.0	
12 hours	1.0 mg SL	7.2 ± 4.6	.050†
	0.5 mg SL	5.2 ± 2.0	
	0.25 mg SL	2.1 ± 1.1	
	1.0 mg PO	6.8 ± 3.6	
	0.5 mg PO	3.6 ± 1.9	
24 hours	1.0 mg SL	3.1 ± 1.7	.172
	0.5 mg SL	2.0 ± 1.2	
	0.25 mg SL	0.9 ± 0.8	
	1.0 mg PO	2.3 ± 1.3	
	0.5 mg PO	0.9 ± 0.6	

SD = standard deviation; SL = sublingual; PO = oral.
* P values from repeated measures analysis of variance.
† See results in the text for significant differences within groups.

Discussion

Sublingual administration of micronized 17β-estradiol results in a rapid absorption of E2 through the oral mucosa directly into the systemic circulation. Within the first hour of administration there is a rapid peak of E2 concentration, and then E2 levels decrease because of the metabolism to E1, with E2 levels returning to less than 60 pg/mL by 6 hours. With comparable dosing, sublingual administration yields higher E2 levels than does oral administration. Estrone levels are highest at 3–4 hours and have a more gradual rise and fall compared to E2 levels. The ratio of E2 to E1 changes significantly during the 24 hours after sublingual dosing. Initially, a high E2 to E1 ratio is present, and then this ratio decreases as E2 is metabolized.

Oral dosing of micronized 17β-estradiol results in an initial metabolism of E2 to E1 as the drug passes through the gastrointestinal mucosa and directly into the liver via the portal circulation before its access by the systemic circulation.[2] Thus, E2 levels gradually rise to peak at 6–7 hours, but these levels never fluctuate dramatically. Due to first-pass metabolism, E1 levels always exceed those of E2 with oral dosing; thus, there is a high circulating E1 to E2 ratio.

The pharmacokinetic data on oral dosing in this study are similar to those of previously published reports. Lobo and Cassidenti[2] have reported that the administration of 1 mg of micronized E2 resulted in an E2 Cmax of 40–50 pg/mL, an E1 Cmax of 200 pg/mL, and an E1 sulfate Cmax of 20 ng/mL. Kuhnz and colleagues[9] reported pharmacokinetic parameters with oral administration of 2 mg of micronized E2. For E2 they found a Tmax of 8.2 hours and a terminal half-life of 13.5 hours, and for E1 they found a Tmax of 6.3 hours and a terminal half-life of 11.2 hours.

We were able to locate only one report, that of Burnier and associates,[10] dealing with sublingual administration of micronized 17β-estradiol. Their findings included a Cmax for E2 of 773.6 pg/mL and a Cmax for E1 of 384.8 pg/mL after a dosage of 0.5 mg. These values are considerably greater than those found in our study. The reason for this difference is unclear. The study by Burnier et al[10] used a 1-mg tablet of Estrace, which had been precut in half, whereas at the time of our study, the 0.5-mg single tablet was available.

Estrone sulfate circulating levels are severalfold greater than those of either E2 or E1. This metabolite may serve as a large circulating pool of available estrogen to tissues with sulfatase activity.[2] In our study, E1 sulfate levels correlated with the dosage of administered micronized 17β-estradiol. With equivalent dosages, sublingual administration tended to result in higher E1 sulfate levels than did oral administration, but these differences were not statistically significant.

When sublingual administration is compared with oral administration, identical dosing results in higher AUC for E2 administered sublingually; there is little difference in the AUC for E1 according to the route of administration. The higher E2 levels measured after sublingual dosing suggest that this may be a more physiologically potent route of estrogen therapy. There is no question that the potency of estrogen therapy may vary according to the route of administration, type of preparation, and dosage of preparation, but what are the physiologic ramifications of these differences?

Several areas of study demonstrated important differences in physiologic response according to the dose, type, and route of estrogen therapy. The occurrence of vasomotor symptoms correlates with the circulating level of E2, and a dose-dependent response to estrogen replacement therapy has been demonstrated.[11,12] Bone density studies have shown a dose-dependent response in bone resorption with varying doses of orally administered micronized E2.[5,13] The change in lipoprotein levels associated with estrogen therapy is both dose-dependent and variable according to the route of administration. High-density lipoprotein (HDL) increases are dose dependent,[4,14] whereas decreases in low-density lipoprotein (LDL) and increases in HDL are more pronounced with oral conjugated equine estrogen when compared to those from transdermal E2 administration.[4,14,15] Likewise, changes in the liver's production of several proteins, including sex steroid binding globulin, corticosteroid-binding globulin, thyroid-binding globulin, and renin substrate, are dose dependent and result from oral but not non-oral therapy.[4,6,16] In addition, oral therapy increases biliary cholesterol saturation and results in a more lithogenic bile compared to non-oral therapy results.[17] In contrast, non-oral routes of administration, such as transdermal and subcutaneous administration, give more consistent hormone levels than does oral therapy.[3]

Recent studies have demonstrated that estrogen directly affects arterial resistance[18] and effects a clinical improvement in women with non-arteriosclerotic angina.[19] The study of Giuseppe and colleagues[20] has demonstrated the ability of sublingually administered E2 acutely to relieve anginal pain in estrogen-deficient women. Whether the vascular response to estrogen depends on the dose or on the type of circulating estrogen remains to be determined.

The known physiologic reactions to different types and routes of estrogen replacement should be used to individualize therapy. For example, oral therapy may be preferable in women with hypercholesterolemia or in women with decreased HDL levels. Non-oral ther-

apy may be more advantageous in women who smoke, women with hypertriglyceridemia or gallstones, and women with a history of thromboembolic phenomena.

The clinical usefulness and safety of the sublingual administration of micronized E2 need further evaluation. Theoretically, the sublingual form of administration may be more physiologically potent and may be useful in the prevention of osteoporosis and vasospastic phenomena in women with non-atherosclerotic angina or migraine headaches.

On the other hand, the safety of this route of administration also needs to be established. A more potent effect on the endometrium could result in an increased risk of hyperplasia, necessitating a change in the standard progestin treatment protocols. The information about estrogen levels after sublingual dosing obtained in this study may be used in further studies of the clinical efficacy of this route of administration.

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