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A PILOT STUDY OF THE COMPARATIVE BIOAVAILABILITY OF ESTRADIOL FROM TWO DIFFERENT ESTRADIOL TRANSDERMAL SYSTEMS: OESCLIM® 50 AND SYSTEN® 50

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ABSTRACT

The bioavailability of estradiol from Oesclim® 50 and Systen® 50, two matrix-type estradiol transdermal systems with the same nominal delivery rate of 50 μg per 24 hours, was compared in a randomized, crossover pilot study of 12 healthy postmenopausal women. A 7-day washout separated the two 4-day application periods. Serum estradiol levels were determined by using radioimmunoassay before application of the transdermal system and at defined intervals thereafter. Higher serum estradiol levels were observed with Oesclim 50 than with Systen 50. Analysis of log-transformed, baseline-corrected pharmacokinetic values showed significant differences between the two transdermal systems. Except for the maximum serum concentration and concentration at 72 hours, all Oesclim 50 pharmacokinetic values were significantly higher than those of Systen 50 ($P < 0.05$). Estradiol bioavailability was approximately 1.5 to 2 times higher after application of Oesclim 50 than after application of Systen 50.

INTRODUCTION

Natural or surgical menopause is characterized by the depletion of ovarian hormone secretions. Thus menopause results in a gradual decrease in the levels of estradiol, the principal secretion of the ovaries. This estrogen deficiency triggers vasomotor and psychologic disorders in the short term, cutaneomucosal atrophy in the medium term, and vascular and osteoporotic disease in the long term. By mitigating the hormone deficiency, hormone replacement therapy reduces or even eliminates the unwanted effects of menopause. Progress made in estrogen therapy over the last 10 years in both the nature of the compounds used and the routes of administration employed has led to more widespread acceptance of such treatment.[1]

Estrogens are traditionally administered orally. However, estradiol is

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extensively metabolized in the intestinal mucosa to form estrone, which leads to an estradiol:estrone ratio below the physiologic ratio in premenopausal women. In addition, first-pass hepatic metabolism converts estradiol into inactive glucuronide and sulfate conjugates. As a result, the product administered can undergo a partial loss of activity, requiring increased doses of estradiol. Furthermore, evidence indicates that the high concentration of estrogens in the portal circulation alters the synthesis of various proteins, including binding proteins, angiotensinogen, antithrombin II, and lipoproteins.[2] This may be the cause of side effects such as hypertension, thrombosis, and gallbladder disease.[3]

By avoiding metabolic degradation in the intestines and the first-pass effect in the liver, the percutaneous route reduces the dose required; 40 times less estradiol is required by using the percutaneous route than the oral route to obtain the same efficacy over 24 hours.[4] A further advantage is that the estradiol:estrone ratio is maintained at a value much closer to premenopausal levels. Several transdermal delivery systems (patches) for estradiol have been developed that take advantage of this route of administration. The slow release of the active ingredient from the patch directly into the bloodstream provides more stable serum levels than the oral route, and the ease of use may lead to a high degree of patient compliance.[5]

In this study, we compared the bioavailability of estradiol from two different transdermal systems with the same nominal delivery rate of 50 μg per 24 hours: Oesclim® 50, a second-generation, matrix-type transdermal system manufactured and marketed in France by Laboratoires FOURNIER, S.C.A., Dijon, France, and Systen® 50, a matrix-type transdermal system marketed in France by JANSSEN-CILAG S. A., Boulogne-Billancourt, France, and in the United Kingdom as Evorel® by CILAG Ltd, Saunderton, United Kingdom.

SUBJECTS AND METHODS

Twelve healthy postmenopausal women volunteered to participate in this open-label, two-way, randomized, crossover pilot study and provided written informed consent. They ranged in age from 45 to 66 years old, and their weight (average, 67.1 kg) was within 20% of the limits of the scale proposed by the Metropolitan Life Insurance Company.[6,7] All subjects completed all trial procedures.

Postmenopausal status was confirmed by amenorrhea of at least 12 months, serum luteinizing hormone and follicle-stimulating hormone levels >20 IU/L, and estradiol levels <25 pg/mL. All participants had normal cervical smear and breast examination results within the previous 18 months, and all clinical and laboratory variables were within the normal range for healthy subjects or were clinically acceptable.

Exclusion criteria included heavy smoking, history or evidence of alcohol abuse, regular use of addictive drugs such as tranquilizers, and excessive consumption (more than 8 cups per day) of caffeine-containing beverages. Also excluded were subjects with a history of major medical or psychiatric illness or surgery that might put them at risk or modify their metabolism of the study drug, those with any acute or chronic systemic abnormality, those with a history of hypersensitivity to any drug, and those with asthma. Participants were not to have donated blood, taken part in any other drug trial, or have received any treatment affecting hepatic microsomal enzymes during the 3 months preceding the study. Women who had been exposed to estrogens during the 2 months before the study or who were receiving any regular medication were excluded. No medication was permitted during the 48 hours before the application in each dosing period or during the dosing period. Cigarettes and caffeine- or xanthine-containing beverages were not allowed during the trial.

The study protocol was approved by the SIMBEC Independent Ethics Committee, and the trial was conducted in accordance with the Good Clinical Practices.[8]

Each subject was treated with Oesclim 50 and Systen 50. Oesclim 50 is a second-generation, matrix-type transdermal system containing 10 mg of 17 β-estradiol in the matrix, with a nomimal delivery rate of 50 μg per 24 hours. Systen 50 is a matrix-type transdermal system containing 3.2 mg of 17 β-estradiol and releasing approximately 50 μg over 24 hours.

The first transdermal system was applied to the outer upper quadrant of the buttock. After a 7-day washout period, the second transdermal system was applied to the same place on the opposite buttock. Subjects fasted overnight before application of the transdermal system. Lunch was provided 4 hours after application and another meal was provided 8 hours after application. Subjects continued their normal diets from 12 hours after application. Five milliliters of blood was drawn before transdermal system application and at the following times after application: 2, 4, 8, 12, 24, 36, 48, 72, and 96 hours. Daily visual inspections of the transdermal systems were performed to evaluate adhesion. Local skin tolerability was assessed after the transdermal system was removed. Spontaneously reported adverse events were recorded throughout the study and a complete biological evaluation (hematology and biochemistry) was performed at the end of the study.

Serum levels of 17 β-estradiol in the blood samples were determined directly, without extraction, using the Clinical Assays™ Estradiol Radioimmunoassay kit (SORIN BIOMEDICA S.P.A., Saluggia, Italy). The antiestradiol antiserum used in this kit has a very low cross-reactivity (<0.6%) with metabolites of estradiol and with the other main female steroid hormones, ensuring that the assay is highly specific. With each series of assays, sera supplemented with known amounts of estradiol were

analyzed as quality controls. The inaccuracy of the method was always <15% for the range of concentrations between 10 and 400 pg/mL. The limit of quantitation was therefore fixed at 10 pg/mL, which was sufficient, since in the absence of treatment, serum levels of estradiol in menopausal woman are approximately 15 pg/mL.

Pharmacokinetic measurements were derived from the serum estradiol concentration-time profiles after each application in each subject. Values were calculated either using uncorrected data for descriptive analyses or using data corrected for endogenous estradiol for statistical analyses. The estradiol quantities delivered by the transdermal systems were assessed by using C_{max} (maximum observed serum concentration during each transdermal system application in pg/mL) and AUC (area under the serum concentration-time curve calculated by the linear trapezoidal rule in pg/mL · h). For each application, AUC was determined for the periods 0 to 72 hours and 0 to 96 hours after transdermal system application. C_{av} (average serum concentration from time 0 to a defined sampling time point after each application in pg/mL) was determined for the periods 0 to 72 hours and 0 to 96 hours after application. The serum concentrations (in pg/mL) at 72 hours and 96 hours after transdermal system application were recorded as C_{72} and C_{96}. The relative bioavailability of Oesclim 50 (Systen 50 taken as reference) over the 3 days after application was calculated as follows:

$$\frac{AUC_{0-72}\text{ (Oesclim 50)}}{AUC_{0-72}\text{ (Systen 50)}}$$

A similar calculation was performed to determine the relative bioavailability of Oesclim 50 over the 4 days after application using the value AUC_{0-96}. The time at which C_{max} occurred (t_{max}) also was recorded.

Statistical Analysis

Summary statistics (minimum, maximum, mean, and standard deviation) for the estradiol levels of the subjects were obtained for each application at each time point.

Statistical analyses were performed using the general linear model procedure in the SAS® statistical program (SAS Institute, Inc., Cary, North Carolina). Statistical analysis of the predose estradiol serum levels before each transdermal system application (to assess the stability of the baseline values of the two periods) was undertaken using the analysis of variance (ANOVA) technique with repeated measures to account for the period and subjects. Statistical analysis of the pharmacokinetic values determined from serum levels corrected for endogenous estradiol was

undertaken using ANOVA, taking into account subjects, periods, and treatments.

Correction for endogenous estradiol was made using the baseline concentration level obtained just before application of the transdermal system at each period. This baseline value was subtracted from the individual levels obtained during application of each transdermal system. If the concentration before application for a subject was lower than the limit of quantitation (LOQ), this concentration was used for the subtraction, even though it was lower than the LOQ. If, on subtraction, the corrected concentrations became negative, they were set to zero.

The statistical analysis was performed both on non–log-transformed data and on log-transformed data. The 90% confidence interval on the log-transformed data was determined. The values for t_{max} were compared by using the Friedman test. The level of significance was set at $P < 0.05$. Results are given as mean ± SD.

RESULTS

The mean ± SD uncorrected serum estradiol levels determined at each sampling time point after application of Oesclim 50 or Systen 50 for 4 days in the 12 postmenopausal women are shown in Figure 1. The same information (mean only) superimposed for the two products is presented in Figure 2. Higher serum estradiol levels were observed with Oesclim 50 than with Systen 50. After application of Oesclim 50, the mean baseline-uncorrected serum estradiol levels at each time point increased to a peak value of 46.5 ± 33.4 pg/mL at 12 hours. The peak value for Systen 50 at 12 hours was 32.3 ± 17.7 pg/mL.

Mean estradiol pharmacokinetic values (C_{max}, C_{72}, and C_{96}), all uncorrected for endogenous estradiol, are compared in Figure 3. The mean uncorrected C_{max} values were 52.8 pg/mL for Oesclim 50 and 36.0 pg/mL for Systen 50, with mean t_{max} values of 24.3 hours and 21.3 hours, respectively. The mean corrected values for C_{max}, C_{72}, and C_{96} are given in the table. Mean uncorrected values for $C_{av\ 0-72}$ and $C_{av\ 0-96}$ are shown in Figure 4. The mean corrected values are given in the table.

Figure 5 shows the pharmacokinetic values for AUC_{0-72} and AUC_{0-96} calculated from the serum estradiol levels corrected for endogenous estradiol. The bioavailability of estradiol after Oesclim 50 application was higher than that after Systen 50 application. Relative bioavailability ($AUC_{Oesclim\ 50}/AUC_{Systen\ 50}$) was 1.65 and 1.73 from 0 to 72 hours and 0 to 96 hours, respectively, after application.

The table provides a summary of the statistical analysis of log-transformed and baseline-corrected data. Significant differences ($P < 0.05$) were seen between the two transdermal systems. Except for C_{72} and C_{max},

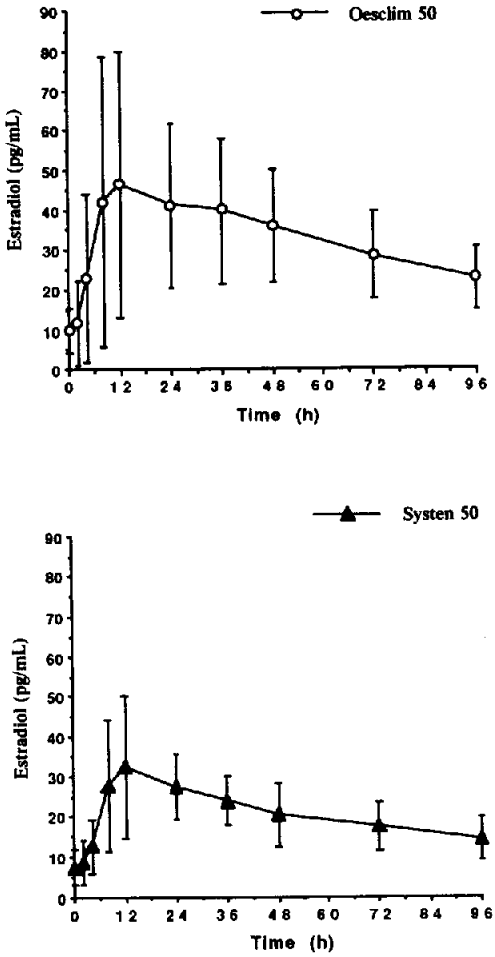

Figure 1. Mean ± SD estradiol serum levels after application of Oesclim® 50 (Laboratoires FOURNIER S.C.A., Dijon, France) or Systen® 50 (JANSSEN-CILAG, Boulogne-Billancourt, France) for 4 days in 12 postmenopausal women.

all Oesclim 50 pharmacokinetic values were significantly higher than those for Systen 50. However, a comparison of mean t_{max} values using the Friedman test indicated no statistically significant difference between Oesclim 50 and Systen 50 (24.3 ± 15.6 hours vs 21.3 ± 18.1 hours, respectively).

Three subjects (25%) experienced a total of three minor adverse events after application of Oesclim 50; these events were mild in severity and included nausea and tiredness. Five subjects (42%) experienced a total of eight minor adverse events after application of Systen 50, including headache, lower abdominal pain, nausea, and vomiting. These were all mild in

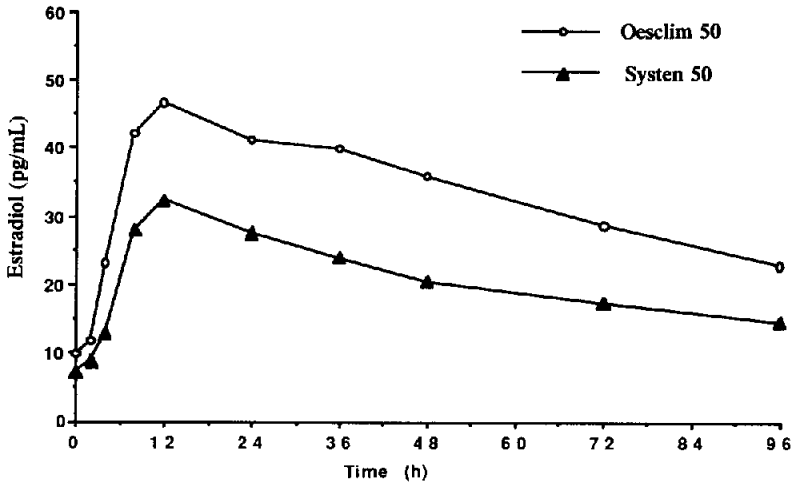

Figure 2. Mean estradiol serum levels after application of Oesclim® 50 (Laboratoires FOURNIER S.C.A., Dijon, France) or Systen® 50 (JANSSEN-CILAG, Boulogne-Billancourt, France) for 4 days in 12 postmenopausal women.

severity except for one case of headache that was considered to be of moderate-to-severe intensity. Three mild skin reactions at the application site were recorded with Oesclim 50 and one with Systen 50. In terms of adhesion, one Systen 50 system became completely detached while the subject was undressing, and another became slightly unstuck at one corner. No signs of detachment were observed with the Oesclim 50 systems.

DISCUSSION AND CONCLUSIONS

Twelve healthy postmenopausal women completed this two-part, balanced, crossover study to compare the bioavailability of estradiol from two transdermal systems, Oesclim 50 and Systen 50, over a 4-day application period. Both transdermal systems have the same nominal delivery rate of 50 μg of 17 β-estradiol per 24 hours.

The serum estradiol profiles produced by these two matrix-type systems were similar. However, the results showed higher serum estradiol levels after application of Oesclim 50 than after application of Systen 50. Except for C_{72} and C_{max}, pharmacokinetic values were significantly higher for the Oesclim 50 system than for the Systen 50 system. The bioavailability of estradiol was approximately 1.5 to 2 times higher after application of Oesclim 50 than after application of Systen 50.

Serum estradiol levels after application of a third type of estradiol transdermal system (Estraderm®, Ciba Pharmaceutical Company, Summit, New Jersey) have been reported.[9,10] In this first-generation system,

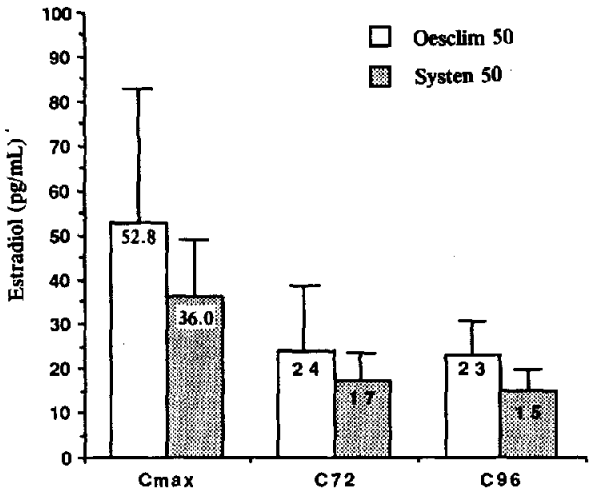

Figure 3. Comparison of mean ± SD estradiol pharmacokinetic values (C_{max}, C_{72}, and C_{96}) after application of Oesclim® 50 (Laboratoires FOURNIER S.C.A., Dijon, France) or Systen® 50 (JANSSEN-CILAG, Boulogne-Billancourt, France) in 12 postmenopausal women. Values are corrected for endogenous estradiol. C_{max} = maximum serum concentration; C_{72} and C_{96} = serum concentrations 72 and 96 hours, respectively, after application.

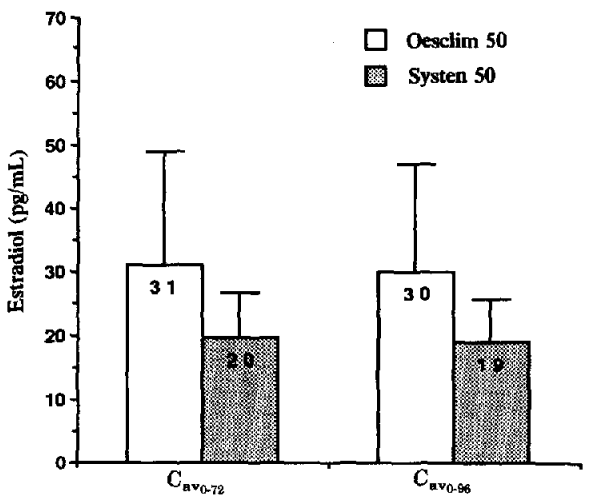

Figure 4. Comparison of mean ± SD estradiol pharmacokinetic values ($C_{av_{0-72}}$ and $C_{av_{0-96}}$) after application of Oesclim® 50 (Laboratoires FOURNIER S.C.A., Dijon, France) or Systen® 50 (JANSSEN-CILAG, Boulogne-Billancourt, France) in 12 postmenopausal women. Values are corrected for endogenous estradiol. C_{av} = average serum concentrations from time 0 to defined sampling time.

Table. Comparison by using analysis of variance of log-transformed and corrected pharmacokinetic values after application of Oesclim® 50* (OES) and Systen® 50† (SYS) in 12 postmenopausal women.

	AUC_{0-72} (pg/mL · h)		AUC_{0-96} (pg/mL · h)		$C_{av\,0-72}$ (pg/mL)		$C_{av\,0-96}$ (pg/mL)		C_{72} (pg/mL)		C_{96} (pg/mL)		C_{max} (pg/mL)		t_{max} (h)	
	OES	SYS	OES	SYS	OES	SYS	OES	SYS	OES	SYS	OES	SYS	OES	SYS	OES	SYS
Mean	1828	1109	2280	1316	21.3	12.6	20.4	12.0	19.4	10.0	12.9	7.2	42.9	28.7	24.3	21.3
Coefficient of variation (%)	61	36	60	32	77	44	75	43	63	46	71	50	69	47	64	85
P	0.0177		0.0117		0.0271		0.0236		NS		0.0404		NS		NS	
90% Confidence interval	1.14–1.81		1.18–1.91		1.11–1.81		1.12–1.82		1.05–2.54		1.11–2.19		1.04–1.71			

AUC = area under the serum concentration-time curve; C_{av} = average serum concentrations from time 0 to defined sampling time; C_{72} and C_{96} = serum concentrations 72 and 96 hours, respectively, after application; C_{max} = maximum serum concentration; t_{max} = time at which C_{max} occurred.

* Trademark: Laboratoires FOURNIER S.C.A., Dijon, France.

† Trademark: JANSSEN-CILAG, Boulogne-Billancourt, France.

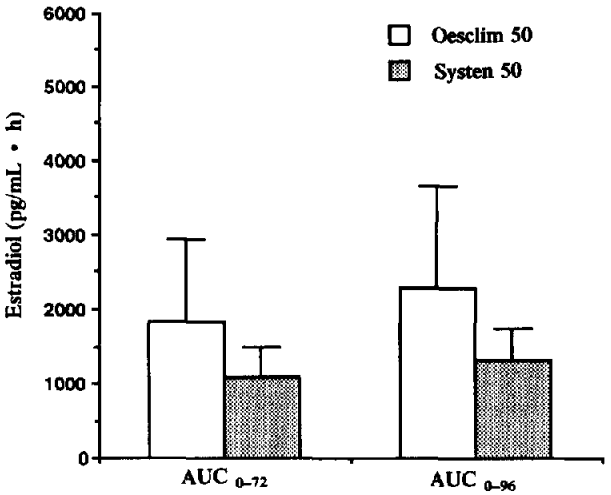

Figure 5. Comparison of mean ± SD estradiol pharmacokinetic values (AUC_{0-72} and AUC_{0-96}) after application of Oesclim® 50 (Laboratoires FOURNIER S.C.A., Dijon, France) or Systen® 50 (JANSSEN-CILAG, Boulogne-Billancourt, France) in 12 postmenopausal women. Values are corrected for endogenous estradiol. AUC = area under the concentration-time curve.

the drug reservoir is a 1 mg/50 mg ethanolic solution of 17 β-estradiol. This pharmaceutical formulation allows a more accurate measurement of nominal delivery rates than a matrix system. For the Estraderm patch size with a nominal delivery rate of 50 μg estradiol per 24 hours, one study measured mean serum levels of estradiol of 39 pg/mL over a 72-hour application period.[9] In another study with the same Estraderm patch size, mean serum estradiol levels after 3 weeks of therapy were reported to be 33 pg/mL.[10] These values can be compared with the uncorrected C_{av} values for Oesclim 50 and Systen 50 measured in this study. For Oesclim 50, C_{av} values over 72 hours and 96 hours were approximately 30 pg/mL, whereas those for Systen 50 were approximately 19 pg/mL. Similarly, for AUC_{0-72}, the mean value for the Estraderm (50 μg/24 hour) system is approximately 2680 pg/mL · h,[9] compared with mean AUC_{0-72} values of 1828 pg/mL · h for Oesclim 50 and 1109 pg/mL · h for Systen 50 in our study. A comparison of results for the three systems suggests that the actual delivery rate of Oesclim 50 is closer to that of Estraderm (50 μg/24 hour) than to Systen 50.

In conclusion, both Oesclim 50 and Systen 50 estradiol transdermal systems were well tolerated and showed good adhesion. Estradiol bioavailability was approximately 1.5 to 2 times higher after application of Oesclim 50 than after application of Systen 50.

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