

Pharmacokinetics of oral micronized β -estradiol in postmenopausal women receiving maintenance hemodialysis

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Background. Although 11% of postmenopausal women with end-stage renal disease (ESRD) are prescribed hormone replacement therapy (HRT), the appropriate use remains poorly explored. Although there remains controversy surrounding the benefits of HRT, it may be of particular interest in this population, which has a high risk of bone loss and a fourfold increase in fracture risk compared to the general population. However, the appropriate dose of estrogen for use in postmenopausal women with ESRD is not known. The objective of this study was to evaluate the steady-state pharmacokinetics of oral micronized β -estradiol in postmenopausal women with ESRD compared with postmenopausal women with normal renal function in order to determine equivalent dosing.

Methods. Six postmenopausal women with ESRD receiving maintenance hemodialysis and 6 healthy postmenopausal controls received 14 days of micronized β -estradiol (1.0 mg for control, 0.5 mg for ESRD). Blood, urine, and dialysate samples were obtained during a dosage interval on day 14. Estradiol, estrone, albumin, and sex-hormone binding globulin (SHBG) concentrations were determined. Free estradiol concentrations were calculated using a previously described method.

Results. Women with ESRD had significantly lower serum albumin ($610 \pm 31 \mu\text{mol/L}$ vs. $684 \pm 83 \mu\text{mol/L}$) and SHBG (78 ± 17 vs. $118 \pm 13 \text{ nmol/L}$) than control subjects. Total clearance of estradiol was not significantly different. Due to difference in binding, free estradiol concentrations were significantly higher in ESRD women ($53.2 \pm 17.7 \text{ pg/mL}$) than control women ($43.5 \pm 8.7 \text{ pg/mL}$), despite receiving 50% of the dose. There was no significant difference in estrone concentrations. Clearance of both estradiol and estrone in the dialysate was minimal.

Conclusion. Women with ESRD should receive approximately 50% of the dose typically prescribed to women without ESRD.

Key words: hemodialysis, hormone replacement therapy, pharmacokinetics.

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Although appropriate indications for estrogen replacement therapy are controversial, 11% of women with end-stage renal disease (ESRD) over 45 years of age are treated with estrogen replacement therapy [1]. Previous reports have suggested that renal failure may alter the pharmacokinetics of estrogen. Ginsburg et al [2] reported that after a single dose of estradiol, serum concentrations of estradiol and estrone were two to three times that of the control, while another investigator reported that urinary excretion of estradiol in men with normal renal function was 78% to 83% over four days compared to 1.4% in men with ESRD [3]. Inappropriately high doses of hormone replacement therapy may result in high levels of estrogen and contribute to the higher risk for endometrial cancer that has been reported among women with ESRD [4, 5]. Other potential risks of estrogen, such as breast cancer, coagulopathy, or risk of coronary artery disease, may also be dose-dependent. Although single dose pharmacokinetic studies have suggested dose modification may be necessary, the steady-state pharmacokinetics of estradiol in women with ESRD have not been studied. If estradiol undergoes nonlinear metabolism or protein binding, the single dose study may underestimate the effects of ESRD and overestimate the determination of an equivalent dose of HRT in ESRD postmenopausal women. Given the recent reports suggesting a slightly higher risk for cardiovascular events among women treated with hormone replacement therapy (HRT), determining the appropriate dose of estrogen replacement is particularly important in the ESRD population [6]. Therefore, the objective of the study was to determine the steady-state pharmacokinetics of oral micronized β -estradiol in postmenopausal women with ESRD compared with postmenopausal women with normal renal function in order to determine equivalent dosing.

METHODS

Study population

Six postmenopausal females with ESRD receiving maintenance hemodialysis at the Northwest Kidney Center, Seattle, Washington, and six postmenopausal females with normal renal function (controls) were recruited from a University of Washington General Internal Medicine Clinic, Seattle, Washington, to participate in the study. Women with ESRD and controls were approximately matched for age (within 3 years) and body mass index [weight (kg)/height (cm²)] \pm 15%. Hemodialysis patients were required to have been stable dialysis patients for greater than 6 months. Nondialysis patients had a serum creatinine of <1.4 mg/dL. All subjects were required to have had their last menstrual period more than 1 year prior to enrollment, a follicle stimulating hormone (FSH) level greater than 40 mIU/mL, normal serum transaminases, and a normal Pap smear and mammogram within 1 year of enrollment. Subjects were excluded if they were currently receiving estrogen therapy, had active liver disease, a history of deep vein thrombosis, a history of breast cancer, a hematocrit less than 27%, or diabetes mellitus requiring insulin.

Study design

All subjects were treated with micronized β -estradiol (EstraceTM) (1.0 mg for control and 0.5 mg for ESRD subjects) for 14 days and medroxyprogesterone acetate (MPA) 2.5 mg/day. On day 14, the subjects were admitted for monitoring to the Clinical Research Unit at the University of Washington. Intravenous access was established for blood sampling. Baseline serum assays were obtained and 24-hour urine collection was initiated. A 1.0 mg dose for control and 0.5 mg dose for ESRD subjects of micronized β -estradiol and 2.5 mg MPA was administered orally. Standard four-hour hemodialysis for subjects with ESRD was initiated at hour four. Among dialysis patients, dialysate samples were collected at 10, 60, 120, 180, and 240 minutes after the start of dialysis. Blood samples were collected at hour 0, 1, 2, 4, 9, 12, 16, and 24 postdose. Blood samples were drawn and spun for serum separation. Serum, urine, and dialysate specimens were frozen at -20°C for storage. After the hour 24 sample the study subjects were discharged from the hospital.

Assays

Estradiol, estrone, albumin, and sex-hormone binding globulin (SHBG) were assayed using commercially available kits. Estradiol concentrations in serum, urine, and dialysate fluids were determined at each of the blood sampling time points using a competitive immunoassay (Assay Designs, Inc., Ann Arbor, MI, USA). The standard curve ranged from 9.6 to 30,000 pg/mL, and sample

concentrations were calculated using a log-linear scale. Estrone concentrations in serum, urine, and dialysate fluids were determined at each of the blood sampling time points by an enzyme immunoassay (ALPCO, Windham, NH, USA). The standard curve ranged from 25 to 2000 pg/mL and sample concentrations were calculated using a log-linear scale. Samples for both estradiol and estrone were diluted sufficiently with assay buffer as needed in order to obtain the concentrations within the standard curve. Serum concentrations of albumin (Sigma Diagnostics, St. Louis, MO, USA) and SHBG (Wako Diagnostics, Richmond, VA, USA) were determined at one time point per subject and assayed by a quantitative, colorimetric method.

Data analysis

Serum concentration of unbound or free estradiol (EE_u) was calculated from total serum estradiol concentrations (EE), albumin (ALB), and SHBG plasma concentrations as previously described by Ginsburg et al [2] using the following equation:

$$EE_u = \frac{EE \times 0.003571}{[(3.14 \times 10^8 \times \text{SHBG}) + (4.21 \times 10^4 \times \text{ALB} \times 100) + 1]}$$

Serum total and unbound estradiol concentration versus time data were analyzed with noncompartmental analysis using standard pharmacokinetic methodology. Area under the concentration-time curve during a steady-state interval (AUC_{ss}) was calculated using the trapezoidal rule. The average steady-state serum concentration (C_{avg}) was calculated as the ratio of AUC_{ss} to the dosage interval. Steady-state oral clearance (Cl/F) was calculated as the ratio of daily dose to AUC_{ss} . The fraction of estradiol excreted (Fe) in the urine was determined as the ratio of amount of unchanged estradiol recovered in the urine during the dosage interval to the interval dose. The renal clearance (Cl_r) was determined as the product of Fe and Cl/F . The dialysis clearance (Cl_D) of estradiol and estrone was determined as the ratio of the amount excreted during the 5-hour dialysate to the midpoint plasma concentration of estradiol or estrone, respectively. Two-sided unpaired t test was used to compare the serum concentrations of albumin and SHBG and the pharmacokinetic parameters between healthy control and ESRD subjects at the $P = 0.05$ level of significance.

RESULTS

Characteristics of the study population are given in Table 1. Age, weight, and serum albumin were similar between women with and without ESRD. Women with

Table 1. Subject characteristics

	Control (1 mg)	ESRD (0.5 mg)	<i>P</i> value
Age years	53 ± 10	63 ± 11	0.13
Weight kg	26.4 ± 3.1	25.3 ± 3.7	0.54
Albumin $\mu\text{mol/L}$	684 ± 83	610 ± 31.4	0.088
SHBG nmol/L	118 ± 24	78 ± 17	0.011

Abbreviations are: ESRD, end-stage renal disease; SHBG, sex-hormone binding globulin.

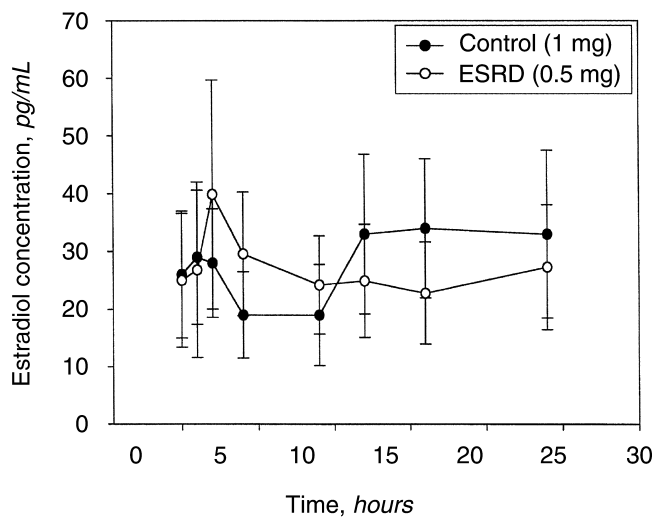


Fig. 1. Estradiol serum concentrations obtained at steady state during one dosage interval for ESRD and healthy control subjects. Mean \pm standard deviations are plotted.

ESRD had significantly lower SHBG than women without ESRD. All women with ESRD had residual renal function.

The total estradiol and estrone serum concentrations during a steady-state dosage interval for control and ESRD subjects are shown in Figures 1 and 2, respectively. In the healthy control subjects, serum concentrations of estradiol exhibited a secondary peak within the 24-hour dosage interval, which was not noted in the ESRD subjects. The average steady serum concentration of estradiol was approximately the same in women with ESRD compared to controls, in spite of having received one-half less estradiol. In spite of receiving one-half the daily dose of estradiol, average steady-state concentrations of estrone were similar but variable, and free estradiol serum concentrations were higher in the ESRD subjects than in the healthy control subjects.

The unbound or free estradiol serum concentrations are depicted in Figure 3. The higher free estradiol concentrations are predominately due to the significantly lower serum concentrations of SHBG and a trend toward lower albumin concentration (Table 2). There was significantly decreased renal clearance of estradiol in ESRD

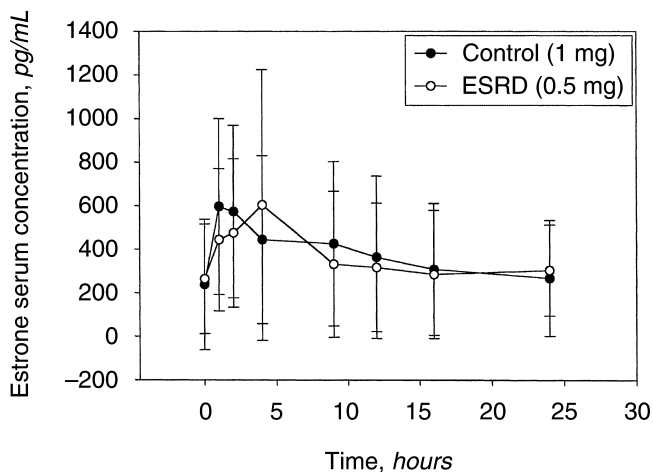


Fig. 2. Estrone serum concentrations obtained at steady state during one dosage interval for ESRD and healthy control subjects. Mean \pm standard deviations are plotted.

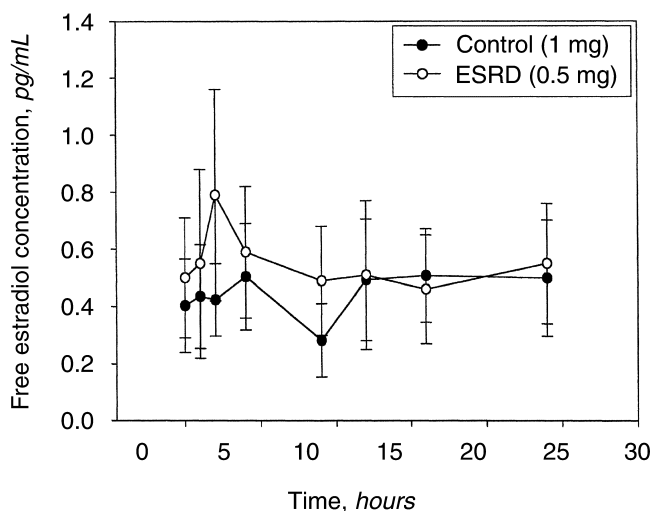


Fig. 3. Free estradiol serum concentrations obtained at steady state during one dosage interval for healthy control subjects and ESRD subjects. Mean \pm standard deviations are plotted.

patients. However, the total clearance of estradiol was not significantly different due to the small fraction of estradiol excreted unchanged by kidneys in both the ESRD and control women. Clearance of estradiol and estrone during dialysis was also minimal, with less than 2% of the dose of estradiol excreted as estradiol and estrone. The fraction of estradiol and estrone excreted unchanged in the urine and dialysate was less than 0.001% of the estradiol dose for the control and renal dialysis patients.

DISCUSSION

The free estradiol serum concentrations among postmenopausal women with ESRD were more than 20%

Table 2. Mean \pm standard deviation (and range) of pharmacokinetic parameters

	Control 1 mg	ESRD 0.5 mg	<i>P</i> value
Estradiol Cl total <i>mL/min/kg</i>	367 \pm 106 (233–492)	279 \pm 163 (155–504)	0.30
Estradiol <i>C</i> _{avg} <i>pg/mL</i>	28.6 \pm 6.6 (23.5–41.4)	23.4 \pm 9.7 (11.1–34.4)	0.35
Free estradiol <i>C</i> _{avg} <i>pg/mL</i>	0.44 \pm 0.09 (0.35–0.62)	0.53 \pm 0.18 (0.19–0.67)	0.03
Estrone <i>C</i> _{avg} <i>pg/mL</i>	376 \pm 338 (118–910)	373 \pm 325 (159–977)	0.99
Estradiol			
Cl renal <i>mL/min/kg</i>	0.057 \pm 0.0052	0.0015 \pm 0.002	0.035
Cl _D dialysis <i>mL/min/kg</i>	NA	0.10 \pm 0.06	
Estrone			
Cl _D dialysis <i>mL/min/kg</i>	NA	0.53 \pm 0.845	

Cl is clearance; *C*_{avg} is average serum concentration; Cl_D is dialysis clearance.

higher than among control women, despite the reduction in dose of β -estradiol of 50%. It is likely that the higher steady-state levels of estrogen are due to decreased catabolism of estradiol. Data suggest that estrogen is metabolized by the liver, metabolites are excreted in the urine, and that clearance is delayed in ESRD patients [3].

Among women with ESRD, this secondary peak in the estradiol concentration time curve did not occur. Estradiol undergoes extensive first-pass metabolism in the liver to the less active estrone and estriol [7]. There is also significant enterohepatic recirculation, which may explain the secondary peak in the estradiol concentration time curve seen in the control population [7]. A potential explanation may be decreased enterohepatic recirculation among women with ESRD.

Both the control and women with ESRD women were treated with concomitant MPA and estrogen. Therefore we were not able to rule out an interaction between ESRD, estradiol, and MPA. However, the results of the study remain clinically relevant since the use of combination therapy is standard care among women with an intact uterus.

After two weeks of treatment in our study, the women with ESRD had lower SHBG than the control women. Prior reports have had seemingly conflicting results. Several studies in postmenopausal women with normal renal function have shown an increase in SHBG concentration of about 45% with oral estradiol after 3 months, but transdermal or vaginal routes of delivery do not raise the plasma SHBG concentration [8–10]. Ginsburg et al [2] reported higher levels of SHBG in women with ESRD than in control women who were not taking estrogen replacement (67 nmol/L vs. 42 nmol/L), and the concentrations of SHBG did not change within 24 hours after oral estrogen. In a longer trial of oral estradiol, 2 mg/day for 8 weeks in women with ESRD, the SHBG increased from 62 to 95 nmol/L; however, this study did not have a comparison population [11]. In the current study, comparison of the effect of oral estradiol administration on the concentration of SHBG was not possible, as SHBG was not measured at baseline. It is possible

that the concentration of SHBG is increased by oral estradiol in all women, and simply increased to a lesser extent in the ESRD patients. Further studies are needed to determine if women with ESRD have subnormal synthetic rates of SHBG.

Our data suggest that dosing modifications are necessary among women with ESRD. Inappropriately high doses of hormone replacement therapy may contribute to the higher risk for endometrial cancer, an estrogen-dependent cancer, reported among women with ESRD [4]. It is also possible that inappropriately high doses of estrogen may place women at higher risk for thrombosis. Hormone replacement therapy has been associated with a higher risk for venous thrombosis [12] and may induce a hypercoagulable state [13]. A hypercoagulable state may lead to an increased risk of vascular access thrombosis and pulmonary embolus, both complications for which ESRD patients are at particularly high risk. Other risks of estrogen therapy include breast cancer, increased incidence of coronary artery disease [6], and gallstones [14]. Although dose-response data on these risks are limited, it is plausible that higher doses would increase the risks.

The use of hormone replacement therapy among women without ESRD has become increasingly controversial. The recent report from the Women's Health Initiative (WHI) has documented significant reductions in hip fracture and colorectal cancer rates among postmenopausal women [6]. Although estrogens have been reported to improve the lipid profile by increasing high-density lipoproteins and decreasing low-density lipoproteins [15], the WHI did not find an overall benefit among those receiving both estrogen and progesterone [6]. Results from the ongoing WHI trial assessing estrogen alone among women without an intact uterus are not yet available. The risks and benefits of HRT among women with ESRD are even less clear. Women with ESRD have a markedly increased fracture risk [16], and although it has not been studied, it is possible that estrogen replacement could also improve the fracture risk in this population. In addition, women with ESRD have markedly abnormal lipid values [17, 18] that improve with estrogen replace-

ment [11]. The effects of estrogen on cardiovascular disease remain unclear, but it is possible that effects would be different in women with ESRD, since improvement of the lipid profile may have a relatively greater benefit. Although these issues are not addressed by the current research, results from this study suggest that future investigations in women with ESRD should use lower doses of estrogen than used in women with normal renal function.

CONCLUSION

Free estradiol serum concentrations among postmenopausal women with ESRD requiring maintenance hemodialysis were more than 20% greater than among women with normal renal function, in spite of reducing the dose of β -estradiol by 50%. These data suggest that women with ESRD should receive a 50% to 70% lower dose of β -estradiol to achieve equivalent concentrations. Measurement of estradiol levels and possibly FSH levels may be of value in selected postmenopausal women with end-stage renal disease receiving HRT. It is likely that any benefit would be relative to the blood concentration and not the actual dose, and there may be potential harm in having excessively high blood concentrations. Future studies should address whether dose modifications of estrogen are necessary among women with chronic kidney disease.

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