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EDITORIAL

Parenteral versus oral treatment of postmenopausal women with estrogen

Estrogens used to treat postmenopausal women are administered by oral and parenteral routes. The most commonly used parenteral routes include percutaneous (by patch, cream or gel) and intravaginal (by cream, gel, tablet, or ring). Each route of administration has advantages and disadvantages.

Two beneficial effects of oral estrogens that are commonly stated are ease of administration and an overall favorable impact on the lipoprotein profile. Ease of estrogen administration may be important in patient compliance when compared with other routes such as intravaginal administration. The lipoprotein profile is considered to be beneficial overall with oral estrogen because plasma low-density lipoprotein cholesterol levels decrease, whereas plasma high-density lipoprotein cholesterol levels increase.[1,2] These effects have been demonstrated in a number of studies, mostly with 0.625 mg conjugated equine estrogens (CEEs). However, despite the expected beneficial changes in lipoprotein profiles obtained in randomized, controlled trials, these changes were not accompanied by the anticipated decrease in cardiovascular risk.[3-5] The reasons for this discordance are unclear.

Disadvantages of oral estrogen use include the following: daily dosing, requirement of a relatively high dose compared with doses used parenterally, variation in intestinal absorption, alteration in hepatic proteins, increase in plasma triglyceride levels. Elevation of triglyceride levels with oral estrogen could be an important concern because elevated triglycerides are a well-recognized risk factor for cardiovascular disease. Women with hypertriglyceridemia may develop severe hyperlipemia on oral estrogen therapy,[6] which may lead to serious adverse effects.

The effect of oral estrogen on hepatic first-pass metabolism may also be an important concern due to the alteration of estrogen-sensitive protein levels, as the highly concentrated estrogen in splanchnic blood is presented to the hepatocytes. A variety of proteins are altered; they include sex hormone–binding globulin (SHBG), corticosteroid-binding globulin (CBG), thyroid-binding globulin (TBG), inflammation markers, as well as markers of coagulation and fibrinolysis. The increases in SHBG, CBG, and TBG are dose dependent, resulting in corresponding decreases in the free fractions of the hormones that they bind, specifically free testosterone, free cortisol, and free thyroxine, respectively. The decreased levels of these hormones have an important clinical relevance. For example, there is a growing body of evidence suggesting that serum testosterone levels have an influence on the sexual functioning of naturally and surgically postmenopausal women. By reducing free testosterone levels, orally administered estrogen may affect sexual function adversely. Also, decreases in free cortisol may be problematic in women with adrenal disease. In addition, lower free thyroxine concentrations in women receiving thyroid replacement may require increases in the dose of thyroxine.

Acute and chronic manifestations of atherosclerosis are now considered by a growing number of investigators as a consequence of a chronic inflammatory process, and certain markers of this process are affected by oral estrogen. Proinflammatory proteins are synthesized by endothelial and smooth muscle cells of large arteries once they are activated by injury. Markers of inflammation in blood include vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), chemoattractant protein-1 (MCP-1), E-selectin, thrombomodulin, interleukin-6 (IL-6), tumor necrosis factor α (TNF-α), and C-reactive protein (CRP). Studies show that orally administered estrogens significantly increase blood levels of CRP, whereas the other inflammatory markers are significantly decreased.[7] These findings support the view that the elevation of CRP by oral estrogen is likely a hepatic first-pass effect of the estrogen. It has been pointed out that elevated CRP may have deleterious effects on vascular inflammation and may contribute to the risk of myocardial infarction observed during the first year of treatment in some randomized and observational clinical studies.[7] However, the uncertainties regarding the clinical significance of CRP levels make it premature to conclude that changes in these levels associated with hormone therapy have a direct clinical consequence.

Oral estrogen also affects hemostasis. Hemostasis is a highly complex process involving two separate but interlinked enzyme cascades, namely, the coagulation and fibrinolytic systems, which regulate the production and breakdown of fibrin, respectively, by checks and balances. The coagulation pathway is normally suppressed by inhibitors, of which tissue factor pathway inhibitor, antiprothrombin III, protein C, and protein S are among the most important. Release of the tissue factor pathway inhibitor initiates the process of coagulation by activating factor VII, which stimulates the conversion of prothrombin to thrombin. The latter protein is the catalyst for the fibrinogen-fibrin

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reaction. Results of the PEPI trial show that oral administration of 0.625 mg of CEEs results in a small but significant reduction in plasma fibrinogen levels in postmenopausal women.[2] This effect was not influenced by addition of medroxyprogesterone acetate (cyclic, 5 mg, or continuous, 2.5 mg) or micronized progesterone (cyclic, 200 mg). However, there is also evidence showing that the coagulation system is activated with oral estrogen. Oral administration of CEEs (0.625 or 1.25 mg) daily decreases levels of thrombin inhibitors, specifically antithrombin III and protein S, and increases indices of thrombin production in a dose-dependent manner.[8] In contrast, there appears to be a beneficial effect of oral estrogen on the fibrinolysis system. The process of fibrinolysis, which involves the enzymatic degradation of fibrin and fibrinogen by plasmin, is initiated by activation of plasminogen to plasmin through the action of tissue plasminogen activator. The latter compound is inhibited by plasminogen activator inhibitor type 1. Studies show that oral CEEs decrease plasminogen activator inhibitor type 1 levels, suggesting an enhanced potential for fibrinolysis with oral estrogen.[7]

In addition to the pharmacodynamic effects resulting from the hepatic first pass of oral estrogen, profound pharmacokinetic effects are also found. For example, following oral administration of 1 mg micronized estradiol (E_2) in postmenopausal women, serum levels of E_2 are approximately 30 to 50 pg/mL, whereas estrone (E_1) levels are several fold higher (150-300 pg/mL).[9] In contrast, serum E_1 and E_2 levels achieved by the transdermal E_2 patch are similar, eg, approximately 30 to 65 pg/mL and 40 to 45 pg/mL, respectively, with the 0.05-mg patch.[9] Another example is the markedly elevated serum levels of estrone sulfate (E_1S) found after long-term oral estrogen treatment.[10] After 7 and 15 months of oral treatment with 1 mg of micronized E_2 in postmenopausal women, mean serum E_1S levels as high as 24.9 ng/mL and 38.8 ng/mL, respectively, were obtained. Baseline serum E_1S levels were less than 0.8 ng/mL. Conversely, in the same study,[10] mean serum E_1S levels were 1.8 ng/mL and 3.2 ng/mL after 9 months of treatment with the 0.05-mg/day and 0.1-mg/day patches, respectively. These levels are in the range observed in premenopausal women. Although the clinical relevance of the markedly elevated serum E_1S levels is not known, the high E_1S levels may contribute significantly to E_2 levels found in tissues, eg, the breast, because E_1S can be readily converted by the sulfatase enzyme to E_1, which can then undergo transformation to E_2 through the action of 17β-hydroxysteroid dehydrogenase.

The oral route of estrogen administration may be especially problematic when treating elderly postmenopausal women, eg, older than 65 years of age, due to differences in pharmacokinetic responses to drugs between younger and older postmenopausal women.[11] Oral bioavailability of many drugs is increased in the elderly due to decreased hepatic first-pass metabolism, which results from a decrease in hepatic blood flow in conjunction with a reduction in hepatic drug-metabolizing capacity.[12] It has been shown that the cytochrome P-450 content of human liver specimens is gradually reduced between the ages of 40 and 69 years in women and men and is reduced by approximately 30% after age 70.[13]

Parenteral administration of estrogen also has advantages and disadvantages. One commonly cited disadvantage of the transdermal patch is that it causes local skin irritation. This is especially true of the membrane-based systems. However, the newer matrix dispersal systems do not possess alcohol and therefore are associated with a much lower incidence of skin reactions. Another commonly cited disadvantage of transdermal E_2 administration is that studies show little or no beneficial effect on the plasma lipid/lipoprotein profile with this route of estrogen delivery, in contrast to the oral route. However, as pointed out earlier, the expected beneficial effect of higher high-density lipoprotein cholesterol and lower low-density lipoprotein cholesterol levels in oral estrogen users has not been associated with reduced cardiovascular risk in randomized, controlled trials.[3-5]

Undoubtedly, the most important benefit of parenteral routes of estrogen administration is the avoidance of disadvantageous pharmacokinetic and pharmacodynamic effects that may be produced during the hepatic first pass when estrogens are administered orally. Some of the pharmacokinetic differences between oral and transdermal routes of estrogen administration were noted earlier. As for pharmacodynamic differences, first of all, transdermal E_2 therapy has a negligible effect on SHBG, CBG, and TBG levels, in contrast to the large elevation of these globulins obtained with oral estrogen. Also, triglycerides are not increased by transdermal E_2 administration.[14-17] In addition, transdermal E_2 significantly lowers[18,19] or does not alter[20,21] CRP levels as well as decreases ICAM levels[22] in healthy postmenopausal women. Furthermore, transdermal E_2 does not alter[23] or decrease[24] fibrinogen levels and does not affect factor VII.[20,23] Finally, no change in plasminogen activator inhibitor type 1 levels was observed after 1 month of treatment with a 0.1-mg E_2 transdermal patch,[25] whereas the levels were reduced after 1 year of treatment with a 0.05-mg E_2 patch.[23]

The impact of the route of estrogen administration on venous thromboembolism (VTE) was studied recently in a multicenter case-control study involving postmenopausal women using oral or transdermal estrogen therapy.[26] A total of 271 consecutive cases with a first documented episode of idiopathic VTE and 610 controls, matched for center, age, and admission date, were recruited. The odds ratios for VTE, after adjustment for potential confounding factors, in current users of oral and transdermal estrogen compared with nonusers were 4.2 (95% CI: 1.5-11.6) and 0.9 (95% CI: 0.4-2.1), respectively. The authors concluded that oral but not transdermal estrogen was associated with an increased VTE risk.

Considering that there is a substantial number of estrogenic and progestogenic products used for treatment of postmenopausal women, there are insufficient comparative

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data on pharmacokinetic and pharmacodynamic effects between oral and parenteral routes of administration of these products. The study by Shifren et al[27] in this issue of *Menopause* adds to our knowledge of pharmacodynamic changes induced by oral versus transdermal estrogen therapy on serum binding globulins (SHBG, CBG, and TBG) in naturally postmenopausal women. The results confirm previous findings that show markedly elevated levels of these globulins with oral, but not transdermal, estrogen. More importantly, the present data show that as a consequence of elevations in the concentrations of the binding proteins, oral and transdermal estrogen therapies produce differential effects on total and free concentrations of testosterone, cortisol, and thyroxine. The authors conclude that from a clinical perspective, transdermal estrogen therapy may be preferable to oral estrogen therapy in maintaining free testosterone levels, having little effect on free cortisol levels and minimizing potential interactions with thyroid replacement therapy. A notable strength of the study is the overall sound methodology. Limitations of the study, eg, use of an open-label crossover versus placebo-controlled parallel group study and lack of a second withdrawal period, are well addressed by the authors. Another limitation is that the study is short term. Long-term placebo-controlled studies are needed to compare effects of estrogen treatment between oral and parenteral routes of administration not only on hepatic globulins but especially on markers of inflammation, coagulation, and fibrinolysis. The studies should include different types and doses of estrogen and different regimens when a progestogen is used. Data from such studies should provide us with valuable information about advantages and disadvantages of both routes of administration to allow optimal treatment of postmenopausal women.

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