CP(5

27+
17

CLINICAL REVIEW

M·203NW p1669

Raloxifene hydrochloride

KELLY R. SNYDER, NICOLE SPARANO, AND JENNIFER M. MALINOWSKI

Abstract: The pharmacology, pharmacokinetics, clinical efficacy, adverse effects, and therapeutic role of raloxifene hydrochloride are reviewed.

Raloxifene is a selective estrogen-receptor modulator (SERM) that has been approved for use in the prevention and treatment of osteoporosis in postmenopausal women. A SERM interacts with estrogen receptors, functioning as an agonist in some tissues and an antagonist in other tissues. Because of their unique pharmacologic properties, these agents can achieve the desired effects of estrogen without the possible stimulatory effects on the breasts or uterus. Raloxifene is rapidly absorbed from the gastrointestinal tract and undergoes extensive first-pass glucuronidation. Approximately 60% of a dose is absorbed; however, absolute bioavailability is only 2%. The volume of distribution is 2348 L/kg for a single oral dose of 30–150 mg, and the elimination half-life averages 27.7 hours. In clinical trials in postmenopausal women, raloxifene had an estrogen-like effect on bone turnover and increased bone mineral density. It reduced the risk of fractures in women with osteoporosis. Raloxifene also seemed to reduce the risk of breast cancer and positively influenced blood lipid markers of cardiovascular disease. Raloxifene is generally well tolerated; the most common adverse effects are hot flashes and leg cramps. A serious adverse effect is venous thromboembolism. The recommended dosage is 60 mg/day orally without regard to meals. Ultimately, it will be information on cardiovascular or breast cancer benefits that will determine the future role of raloxifene.

Raloxifene is an alternative to traditional hormone-replacement therapy for the prevention and treatment of osteoporosis in selected postmenopausal women. More study is needed to verify possible benefits related to heart disease and breast cancer.

Index terms: Breast neoplasms; Dosage; Estrogen agonist-antagonists; Mechanism of action; Metabolism; Osteoporosis; Pharmacokinetics; Raloxifene hydrochloride; Toxicity

Am J Health-Syst Pharm. 2000; 57:1669-78

The risks of osteoporosis and cardiovascular disease increase once women reach menopause. Hormone replacement therapy with estrogen can have positive effects in postmenopausal women, including fewer osteoporotic fractures and possible cardiovascular benefits. However, unopposed estrogen treatment is associated with an increased risk of endometrial cancer. In addition, there is still controversy over a possible relationship between estrogen replacement and breast cancer, and many women decline estrogen therapy for that reason.

Raloxifene hydrochloride is a selective estrogen-receptor modulator (SERM) that has been approved for use in the prevention and treatment of osteoporosis in postmenopausal women. Because raloxifene has estrogen agonist-like effects on bone and on cholesterol metabolism and antagonist-like effects on the endometrium and breasts, it has the potential to produce some of the beneficial effects of estrogen without the possible adverse effects. There is still much to be learned about SERMs and their mechanism of action. This article reviews what is currently known about the pharmacology, pharmacokinetics, clinical efficacy, adverse effects, and therapeutic role of raloxifene hydrochloride.

Chemistry

Raloxifene is a benzothiophene

KELLY R. SNYDER, PHARM.D., BCPS, is Assistant Professor, Pharmacy Practice, Wilkes University (WU), Wilkes-Barre, PA, and Clinical Specialist, Family Medicine, Geisinger Health System, Wilkes-Barre. NICOLE SPARANO, PHARM.D., BCPS, is Assistant Professor, Pharmacy Practice, WU, and Clinical Specialist, Family Medicine, Wyoming Valley Family Practice Residency, Kingston, PA. JENNIFER M. MALINOWSKI, PHARM.D., is Assistant Professor, Pharmacy Practice, WU, and Clinical Specialist, Internal Medicine, Department of Pharmacy, Mercy Health Partners, Scranton, PA.

Address reprint requests to Dr. Snyder at the Department of Pharmacy Practice, Wilkes University, SLC 336, Wilkes-Barre, PA 18766, or to snyder@wilkes.edu.

The contributions of Deborah Stier Carson, Pharm.D., BCPS, and James Culhane, Ph.D., are acknowledged.

This is article 204-000-00-012-H01 in the ASHP Continuing Education System; it qualifies for 1.0 hour of continuing-education credit. See page 1676 or http://ce.ashp.org for the learning objectives, test questions, and answer sheet.

H

nonsteroidal derivative that binds to the estrogen receptor.[1,2] It is classified as a selective estrogen-receptor modulator. The chemical name is [6-hydroxy-2-(4-hydroxyphenyl)-benzo[*b*]thien-3-yl]-[4-[2-(1-piperidinyl)ethoxy]phenyl] hydrochloride. The structural formula is shown in Figure 1.

Pharmacology

Raloxifene can be classified as a second-generation SERM. A SERM interacts with estrogen receptors, functioning as an estrogen agonist in some tissues and an antagonist in other tissues. Because of their unique pharmacologic properties, these agents can achieve the desired effects of estrogen without the possible stimulatory effects on the breasts and uterus.[3] For example, while raloxifene mimics estrogen's action on bone and on cholesterol metabolism, it acts as an estrogen-receptor antagonist on the breasts and uterus.

Tamoxifen, which is also considered a SERM, can be classified as a first-generation SERM because, unlike raloxifene, it demonstrates partial agonist activity in the uterus.[4] In other words, not all SERMs are alike; each SERM has unique properties with respect to receptor activity in various tissues. Clomiphene has also been considered a SERM. Information is limited on newer SERMs, such as droloxifene, toremifene, idoxifene, and levormeloxifene.[5]

Understanding the mechanism underlying the selectivity of estrogen-receptor agonist or antagonist activity of SERMs remains an area of research; however, recent advances in our understanding of the estrogen receptor, its subtypes, and its intracellular signaling processes have allowed deeper insight into the pharmacodynamics of SERMs. When an estrogen receptor is activated by a ligand, such as 17β-estradiol, a ligand–receptor complex is formed. This complex then dissociates from a heat-shock protein complex, undergoes dimerization, and subsequently binds to an estrogen response element (ERE) in the promoter areas of different genes. The formation of the estrogen-receptor–DNA complex then stimulates gene transcription. While both 17β-estradiol and raloxifene bind to the same area of the estrogen receptor, the binding affinity, the mechanism of binding, and the alteration of the receptor's structure differ. These differences lead to differential transcriptional effects.[6-8] For example, the estrogen receptor contains two transcriptional activation functions, AF-1 and AF-2.[9] Differential activation of these transcriptional activation functions, as well as various ligand-induced receptor conformations, may be responsible for the tissue-selective effects of SERMs.[7] As a result, the estrogen-receptor–raloxifene complex can bind to DNA sequences distinct from the ERE.

Multiple receptor subtypes, differential subtype activation and antagonism, and selective tissue expression of the subtypes may also account for the differences in the actions of estrogens and SERMs. Originally, it was thought that the estrogen receptor existed in only one form, estrogen-receptor α; however, we now have evidence that a β form exists as well.[10,11] Estrogens and SERMs affect each of these receptors differently.[12] For example, with estrogen-receptor α, 17β-estradiol activates transcription, and with estrogen-receptor β, 17β-estradiol inhibits transcription. This is in contrast to SERMs, which activate with estrogen-receptor β. To add to the complexity, estrogen-receptor α and β messenger RNA (mRNA) levels vary in different tissues. For example, receptor α mRNA has been detected in the uterus, testes, adrenal glands, kidneys, and pituitary; receptor β mRNA has been detected in the ovaries, testes, prostate, spleen, and thymus.[10,11] The extent to which each tissue expresses these receptor subtypes in humans is currently unknown.

Other mechanisms that may explain the unique pharmacologic effects of SERMs include interaction with different coactivators and corepressors in gene transcription, interference of proteins with the estrogen receptor, and estrogen-receptor-independent nongenomic effects.[13-15]

Pharmacokinetics

The pharmacokinetics of raloxifene were investigated in over 1500 women in clinical trials (Table 1).[16] Although most of the women were white and postmenopausal, interpatient variability of approximately 30% was observed.

Absorption. Raloxifene is rapidly absorbed from the gastrointestinal tract and undergoes extensive first-pass glucuronidation. Approximately 60% of an oral dose is absorbed; however, because of extensive presystemic glucuronide conjugation, absolute bioavailability is only 2%. Significant interpatient differences in bioavailability may result from alterations in the rate of glucuronide formation and enterohepatic recycling.[16]

Administration of a single dose of 185 mg of raloxifene hydrochloride to four healthy volunteers resulted in

Figure 1. Chemical structure of raloxifene.

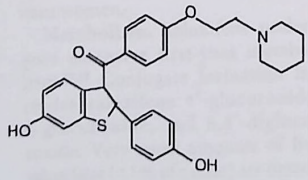

Table 1.
Pharmacokinetics of Raloxifene[16,a]

Dosage Frequency	Mean C_{max}, ng/mL	Mean $t_{½}$ (Range), hr	Mean AUC, ng·hr/mL	Mean CL/*F*	Mean *V*/*F*
Single dose	0.5	27.7 (10.7–273)	27.2	44.1	2348
Multiple doses	1.36	32.5 (15.8–86.6)	24.2	47.4	2853

[a]Data were normalized for dose (in milligrams) and body weight (in kilograms). C_{max} = maximum plasma concentration, $t_{½}$ = half-life, AUC = area under the concentration-versus-time curve, CL = clearance, *F* = bioavailability, *V* = volume of distribution.

a maximum plasma concentration (C_{max}) of 12.5 µg/L within 0.5 hour.[17] The time to maximum concentration of raloxifene varies, depending on the conversion of the drug in the systemic circulation. Administration of the recommended 60-mg dose is expected to result in a mean peak C_{max} of 0.5 ng/mL.[16] Multiple doses of 60 mg are expected to produce a mean C_{max} of 1.36 ng/mL. Although the area under the plasma concentration-versus-time curve (AUC) does not change significantly when multiple doses are given, increasing the dose from 30 mg to 150 mg results in a slight increase in AUC. Administration of raloxifene with a high-fat meal increases C_{max} and AUC by 28% and 16%, respectively, although the effects are clinically insignificant. Therefore, raloxifene may be administered without regard to meals.[16]

Distribution. Raloxifene is widely distributed into tissues; the volume of distribution (V) is 2348 L/kg after administration of a single oral dose of 30–150 mg. V is not dose dependent.[16] Studies with radioactively labeled raloxifene indicate extensive distribution into the liver, serum, lungs, and kidneys. Conversion of the drug to an active metabolite appears to occur in several tissues, including the liver, lungs, spleen, bone, uterus, and kidneys.[16] Raloxifene and its conjugates are 95% bound to albumin and α_1-acid glycoprotein in vitro.[17] Raloxifene does not bind to sex steroid-binding globulin.[16] Although it is unknown whether raloxifene is distributed into breast milk, its high protein-binding profile should theoretically limit such distribution. Nevertheless, lactating women should not use raloxifene. Raloxifene is a pregnancy category X drug and is therefore contraindicated in pregnant women.

Metabolism. Raloxifene undergoes extensive first-pass metabolism.[17,18] Conjugate formation includes raloxifene 4′-glucuronide, 6-glucuronide, and 6,4′-diglucuronide. Very small amounts of free raloxifene (<1% of a dose) are detected in the circulation. The absence of other metabolites suggests that raloxifene is not metabolized by the cytochrome P-450 isoenzyme system.[16] Although raloxifene may be converted back within certain tissues, reconversion to the parent compound does not appear to occur in major target organs, such as the uterus and skeleton. Therefore, it appears that the tissue selectivity of raloxifene is not explained by deconjugation of metabolites to the parent compound in different tissues. The terminal log-linear portions of plasma concentration curves for raloxifene and its conjugates are parallel.

The clearance of raloxifene hydrochloride 400 mg/day given for five days to healthy premenopausal women was 51.5–128.3 L/hr/kg, depending on the phase of the menstrual cycle.[19] A mean steady-state V of 4135 L/kg was observed for the women. There is no evidence to date to suggest significant influences of sex, race, or age (42–84 years) on the clearance of raloxifene.[16]

The half-life ($t_{½}$) of raloxifene at steady state ranges from 15.8 to 86.6 hours and averages 32.5 hours.[16] One study evaluated the $t_{½}$ of raloxifene in 14 healthy postmenopausal women and 14 healthy men.[13] The $t_{½}$ ranged from 11 to 27 hours. The oral clearance of a single dose of raloxifene is 44.1 L/hr/kg. The $t_{½}$ of raloxifene may be prolonged to 27.7 hours, secondary to reverse systemic metabolism and enterohepatic recycling, when the drug is given on a long-term basis.

Elimination. Raloxifene is excreted primarily in the feces.[17] Glucuronide metabolites are eliminated in the biliary tract, and are subsequently broken down by bacteria to the parent drug. Less than 0.2% of raloxifene is excreted unchanged in the urine; less than 6% is excreted in the urine as glucuronide conjugates.

Special populations. *Renal impairment.* Since only a small amount of raloxifene is eliminated unchanged in the urine, there will probably not be studies that specifically address the pharmacokinetics of raloxifene in patients with renal impairment.[16] However, clinical studies have not revealed any differences in the concentration of raloxifene or its conjugates between patients with creatinine clearance as low as 23 mL/min and controls with normal renal function.

Hepatic impairment. Patients with hepatic impairment (Child-Pugh class A with cirrhosis and a total bilirubin concentration of 0.6–2 mg/dL) have plasma raloxifene concentrations that are 2.5 times higher than those of healthy subjects.[16] Increased bilirubin concentrations are correlated with increased plasma raloxifene levels. Experience with raloxifene in patients with hepatic impairment is limited; additional monitoring is recommended.

Clinical trials

Effects on bone. Draper et al.[20] studied the effects of raloxifene on biochemical markers of bone turnover. In this randomized, double-blind, multicenter trial, 251 postmenopausal women received placebo, raloxifene hydrochloride 200 or 600 mg/day, or conjugated estrogens 0.625 mg/day. Bone turnover, measured by serum alkaline phosphatase, serum osteocalcin, urinary pyridinoline cross-links, urinary calcium excretion, and urinary hydroxyproline, was determined at baseline and at two, four, and eight weeks. The estrogen group and both raloxifene groups had similar decreases in all the markers of bone turnover except urinary hydroxyproline (and the difference was not significant among any of the treatment groups). Other than serum osteocalcin in the raloxifene hydrochloride 200-mg/day group, the markers were all significantly different compared with the placebo group. The authors concluded that raloxifene appears to exert an estrogen-like positive effect on the markers of bone turnover. However, this was only a short-term trial; the long-term clinical effects of raloxifene on the skeleton remain to be established.

In an open trial, Heaney and Draper[21] compared raloxifene with estrogen (given as hormone replacement therapy). Postmenopausal women were randomly assigned to estrogen (n = 14), raloxifene (n = 13), or no treatment (n = 6). Raloxifene

hydrochloride was given at 60 mg/day and conjugated estrogens at 0.625 mg/day (plus 5 mg of medroxyprogesterone daily for the first two weeks of each month). Bone-remodeling studies (involving calcium tracer kinetic methods under a constant diet and full-metabolic-balance conditions) were performed at baseline, after 4 weeks of treatment, and after 30–32 weeks of treatment. Bone resorption was significantly decreased in both the raloxifene and estrogen groups after 4 weeks; however, at 31 weeks, remodeling suppression was greater for estrogen than for raloxifene (although remodeling balance was the same for the two agents) (Figure 2). There were no significant changes in the untreated group. The authors concluded that raloxifene acts on the bone-remodeling apparatus as an estrogen agonist, inducing a positive shift in the calcium balance.

Figure 2. Effect of raloxifene on bone resorption.[21]

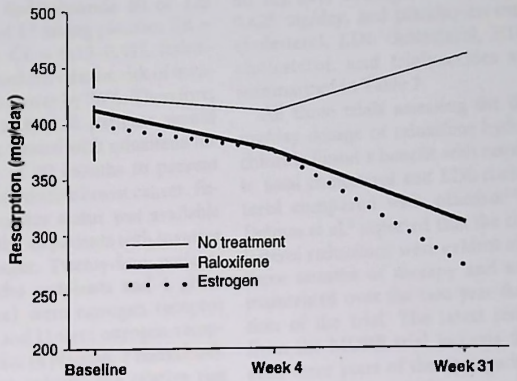

Table 2.
Effects of Raloxifene on Bone Mineral Density[2]

	Mean ± S.D. % Change in Bone Density from Baseline			
		Raloxifene Hydrochloride		
Site	Placebo	30 mg/Day	60 mg/Day	150 mg/Day
Lumbar spine	−0.8 ± 0.3	1.3 ± 0.3	1.6 ± 0.3	2.2 ± 0.3
Hip	−0.8 ± 0.3	1.0 ± 0.2	1.6 ± 0.2	1.5 ± 0.2
Femoral neck	−1.3 ± 0.3	0.6 ± 0.3	1.2 ± 0.3	1.5 ± 0.5
Total body	−0.6 ± 0.2	1.2 ± 0.2	1.4 ± 0.2	1.9 ± 0.4

The effects of raloxifene on bone mineral density were studied by Delmas et al.[2] This double-blind, multicenter trial enrolled 601 postmenopausal women, each having had a lumbar-spine bone mineral density between 2.5 standard deviations below and 2.0 standard deviations above the mean value for normal premenopausal women. These women were randomly assigned to raloxifene hydrochloride 30, 60, or 150 mg or placebo once daily for 24 months. All the women also received a daily supplement of elemental calcium 400–600 mg. At the end of the 24 months, markers of bone turnover had decreased and bone mineral density had increased significantly in the lumbar spine, total hip, femoral neck, and total body with all dosages of raloxifene. For example, the 60-mg/day dosage increased bone mineral density by 1.2% at the femoral neck, 1.6% at the spine and total hip, and 1.4% for the total body (Table 2). There was bone loss at each site in the women given placebo. However, while raloxifene's effects on bone mineral density were significant, they were less than those previously reported for estrogens or alendronate.

Lufkin et al.[22] conducted a one-year double-blind trial in 143 postmenopausal women with osteoporosis. All the women had at least one prevalent vertebral fracture and a low bone mineral density. The patients were randomized to parallel groups receiving no drug (control) or raloxifene hydrochloride 60 or 120 mg/day. All the women also received 750 mg of elemental calcium and vitamin D 800 IU/day. Evaluations were conducted at baseline and at 1, 6, and 12 months. During the year, markers of bone turnover (serum bone alkaline phosphatase, serum osteocalcin, and urinary C-telopeptide fragment of type I collagen/creatinine ratio) were significantly lower in the raloxifene groups. Bone mineral density increased significantly in the total hip in the 60-mg/day group and in the ultradistal radius in both raloxifene groups. There were nonsignificant trends toward increases in bone mineral density in the lumbar spine, total body, and total hip in the 120-mg/day group. Although raloxifene had beneficial effects on bone, the effects were smaller than with estrogen therapy.

The most recent data on raloxifene's effects on bone come from the Multiple Outcomes of Raloxifene Evaluation (MORE) trial.[23] The MORE trial was a double-blind, multicenter clinical trial that looked at raloxifene and the risk of fractures in 7705 postmenopausal women with osteoporosis. All women were randomized to receive placebo or 60 or 120 mg of raloxifene hydrochloride daily. The women were also grouped according to whether or not they had a history of fractures. All the women received calcium 500 mg/day and vitamin D 400 IU/day. After 36 months, radiographs were available for 6828 women. Of these, 503 (7.4%) had at least one new vertebral fracture, including 10.1% of the women in the placebo group, 6.6% of the women receiving 60 mg of raloxifene hydrochloride, and 5.4% of the

women receiving 120 mg. The risk of vertebral fracture was reduced in both raloxifene groups (relative risk [RR] = 0.7 and 95% confidence interval = 0.5–0.8 for the 60-mg group, and RR = 0.6 and 95% CI = 0.4–0.7 for the 120-mg group). There was no significant difference between the raloxifene groups and the placebo group in the risk of nonvertebral fracture. Raloxifene hydrochloride increased bone mineral density in the femoral neck by 2.1% (60 mg) and 2.4% (120 mg) and in the spine by 2.6% (60 mg) and 2.7% (120 mg) ($p < 0.001$ for all comparisons). It appears that three years of raloxifene treatment preserves bone density, reduces bone turnover, and reduces the rate of vertebral fracture in postmenopausal women with osteoporosis.

Effects on breast tissue. *Treatment of breast cancer.* In a Phase II trial, Buzdar et al.[24] studied the effects of raloxifene 200 mg/day in 14 women with disseminated breast cancer with primary or secondary resistance to tamoxifen therapy. All the study patients had discontinued endocrine therapy and chemotherapy for at least four weeks before raloxifene treatment began and were showing signs of progressive breast disease. The patients received raloxifene for up to eight months, but there were no responses (either complete or partial). In fact, disease progression was seen in eight patients.

Prevention of breast cancer. The MORE investigators also studied the occurrence of breast cancer as a secondary endpoint.[25] When breast cancer was suspected, it was confirmed by an oncology review board consisting of five physicians and a pharmacologist who were blinded to treatment assignment. Participants were followed up for a median of 40 months. Breast cancer frequency was examined with an intention-to-treat analysis. Of 7705 women in the study, 54 were found to have breast cancer. Ductal carcinoma in situ occurred in 12 patients (5 receiving placebo, 3 raloxifene hydrochloride 60 mg/day, and 4 raloxifene hydrochloride 120 mg/day), and 40 had invasive carcinoma (13 patients taking raloxifene hydrochloride 60 or 120 mg/day and 27 taking placebo; RR = 0.24, 95% CI = 0.13–0.44). Raloxifene reduced the relative risk of invasive breast cancer by 76%. Therefore, approximately 126 patients would have to be treated with raloxifene for a median of 40 months to prevent one case of invasive breast cancer. Estrogen-receptor status was available for 35 of the 40 patients with invasive breast cancer. Twenty-four patients (20 placebo recipients and 4 given raloxifene) were estrogen-receptor positive, and 11 were estrogen-receptor negative (4 placebo, 7 raloxifene). Raloxifene reduced the relative risk of invasive, estrogen-receptor-positive breast cancer by 90% (RR = 0.10, 95% CI = 0.04–0.24). The large reduction in relative risk seen with raloxifene was due primarily to a reduction in estrogen-receptor-positive breast cancer.

Currently, the Study of Tamoxifen and Raloxifene (STAR) trial is comparing the potential breast cancer benefits of tamoxifen and raloxifene. This trial will enable us to better understand the true benefits of these drugs with respect to breast cancer.

Effects on lipids. Raloxifene appears to positively influence blood lipid markers of cardiovascular disease. Data from clinical trials suggest that raloxifene is similar to estrogen therapy in that it lowers total-cholesterol and low-density-lipoprotein (LDL) cholesterol concentrations compared with placebo.[2,20,22,26] However, unlike estrogen, raloxifene has neutral effects on triglycerides and high-density-lipoprotein (HDL) cholesterol. It has been proposed that the lipid alterations produced by raloxifene hydrochloride 60 mg/day most closely resemble the lipid effects of tamoxifen 20 mg/day (as the citrate); however, data from comparative trials are not available to date.[2,27]

Reductions in total and LDL cholesterol have been documented with raloxifene hydrochloride dosages ranging from 30 to 600 mg/day. The duration of treatment ranged from eight weeks to three years. Comparative data on the effects of raloxifene hydrochloride 60 mg/day, conjugated estrogens 0.625 mg/day, and placebo on total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides are summarized in Table 3.

All three trials assessing the 60-mg/day dosage of raloxifene hydrochloride found a benefit with respect to total cholesterol and LDL cholesterol compared with placebo.[2,12,26] Delmas et al.[2] reported that the cholesterol reductions were evident after three months of therapy and were maintained over the two-year duration of the trial. The latest results from the MORE trial indicate that, after three years of therapy, patients treated with 60 or 120 mg of raloxifene hydrochloride per day are less likely to develop hypercholesterolemia than patients given placebo (2.2% and 1.9% for raloxifene hydrochloride 60 and 120 mg/day and 4.7% for placebo, $p < 0.001$).[25] However, baseline differences in lipid values among the three groups were not reported. Walsh et al.[26] found that raloxifene hydrochloride 60 mg/day reduced lipoprotein (a) levels significantly compared with placebo (by 7%); however, estrogen therapy produced a significantly greater reduction (19%) than either raloxifene or placebo.

Whether these lipid effects equate to a reduction in cardiovascular morbidity and mortality will remain unclear until there are more data. Furthermore, the positive effect of estrogen on cardiovascular disease may be secondary to other favorable effects, such as reduced arterial vasoconstriction and improvements in insulin and glucose metabolism.

The Raloxifene Use for the Heart (RUTH) trial is being conducted to examine the effects of daily raloxifene therapy on the frequency of coronary death and nonfatal myocardial infarction. The study began in 1998 and will continue for seven years.

Effects on endometrial tissue. Raloxifene, in contrast to estrogen and tamoxifen, apparently does not induce endometrial tissue proliferation in postmenopausal women.[1,2,23]

Table 3.
Effects of Raloxifene Hydrochloride 60 mg/Day and Conjugated Estrogens 0.625 mg/Day on Blood Lipids in Postmenopausal Women

Ref.	No. Pts. and Treatment Duration	% Change from Baseline[a]									
		Total Cholesterol			LDL Cholesterol			HDL Cholesterol			Triglycerides		
		P	R	E	P	R	E	P	R	E	P	R	E
2	n = 601, 2 yr	−1.2 ± 0.8	−6.4 ± 1.1[b]	NA	−1.0 ± 1.5	−10.1 ± 1.4[b]	NA	−4.7 ± 1.1	−3.7 ± 0.8	NA	0.0 ± 2.1	3.2 ± 3.1	NA
22	n = 143, 1 yr	−2.8 ± 1.4	−7.0 ± 1.5[b]	NA	−3.7 ± 1.9	−11.4 ± 2.3[b]	NA	−0.8 ± 1.8	4.7 ± 2.1	NA	0.4 ± 4.6	1.5 ± 7.4	NA
26	n = 390, 6 mo	NA	NA	NA	1.0 ± 3.0	−11.0 ± 2.0[c]	−13 ± 1.0[c]	1.0 ± 2.0	1.0 ± 2.0[d]	11.0 ± 2.0	0.0 ± 2.0	−4.0 ± 2.0[d]	20 ± 5.0[c]

[a]Median ± S.D. for references 2 and 26 and mean ± S.D. for reference 22.
P = placebo, R = raloxifene, E = conjugated estrogens, NA = not available.
[b]Significantly different from corresponding value for placebo ($p < 0.05$).
[c]Significantly different from corresponding value for placebo ($p < 0.01$).
[d]Significantly different from corresponding value for conjugated estrogens ($p < 0.001$).

A dosage of up to 150 mg/day did not produce significant differences in endometrial thickness (as measured by transvaginal ultrasound) from baseline or placebo at any six-month test interval over two years.[2] Information from the three-year MORE trial mirrors these results.[23] Of 1781 women who underwent a baseline and at least one follow-up transvaginal ultrasound examination, had trace amounts of fluid in the endometrial space. Fifty-two (31%) of these women had follow-up endometrial biopsies, none of which revealed endometrial hyperplasia or endometrial carcinoma.

Boss et al.[1] compared raloxifene hydrochloride at dosages up to 600 mg/day (or up to 10 times the recommended dosage) with unopposed conjugated estrogens 0.625 mg/day or placebo for eight weeks in 208 postmenopausal women. Significant endometrial stimulation was noted in the estrogen group compared with the placebo and raloxifene groups, whose patients did not show any evidence of endometrial thickening.

Raloxifene may be associated with a lower risk of endometrial cancer than tamoxifen and estrogen. However, the longest trial lasted only three years, so more information is needed to characterize the long-term adverse effects of raloxifene.

Adverse effects

Raloxifene was well tolerated in most of the clinical trials. Common adverse effects were hot flashes and leg cramps. In the MORE trial, hot flashes prompted study withdrawal in 0.1%, 0.7%, and 0.5% of the women in the placebo and the 60- and 120-mg/day raloxifene hydrochloride groups, respectively.[23] The frequencies of breast tenderness and vaginal bleeding did not differ significantly from those for placebo.[2,23,26]

The most serious adverse effect associated with raloxifene treatment is venous thromboembolism. Women in the MORE trial who received raloxifene had three times as many cases of venous thromboembolism as placebo recipients (95% CI, 1.5–6.2), and it was estimated that one case would occur for every 155 women treated with raloxifene for three years.[23]

Drug interactions

Approximately 95% of a dose of raloxifene is bound to plasma proteins. Raloxifene does not affect the binding of phenytoin, tamoxifen, or warfarin in vitro but should be used with caution with other highly protein-bound drugs, including indomethacin, naproxen, ibuprofen, and diazepam. Raloxifene, like estrogen, undergoes enterohepatic cycling, and peak concentrations of raloxifene may be affected by coadministration with antimicrobials. Coadministration of ampicillin with raloxifene reduces peak raloxifene concentrations and absorption by 28% and 14%, respectively. Because systemic exposure and the rate of elimination of raloxifene are not affected, the interaction between ampicillin and raloxifene does not appear to be clinically significant. Cholestyramine reduces the absorption and enterohepatic cycling of raloxifene by 60%. Therefore, concomitant administration of cholestyramine and raloxifene should be avoided. Patients must be closely monitored when taking warfarin with raloxifene because there is a 10% decrease in prothrombin time. Table 4 lists all known drug interactions involving raloxifene.[16]

Dosage and administration

Raloxifene is indicated for use in the prevention and treatment of osteoporosis in postmenopausal women and is available as 60-mg, unscored, white, film-coated elliptical tablets. The recommended dosage is 60 mg/day without regard to meals. Raloxifene is not indicated for combination treatment with estrogen or alendronate.[16]

Patient information

Patients should be informed that raloxifene is not a substitute for maintaining adequate calcium and vitamin D intake or for regular, weight-bearing exercises. Eliminating risk factors for osteoporosis, such as

Table 4.
Drug Interactions Involving Raloxifene

Drug	Description of Interaction
Ampicillin	Peak raloxifene concentration and raloxifene absorption reduced 28% and 14%, respectively
Cholestyramine	Absorption and enterohepatic cycling of raloxifene reduced 60%
Warfarin	Prothrombin time reduced 10%

cigarette smoking, is also important in preventing further bone loss. Because hot flashes are an adverse effect of raloxifene, this agent is not an appropriate choice for postmenopausal women having hot flashes as a primary symptom of estrogen deficiency. Patients taking raloxifene should be told to discontinue the medication 72 hours before surgery or a sedentary period in order to decrease the risk of venous thromboembolism.

Role in therapy

Raloxifene carries FDA-approved labeling for use in the prevention and treatment of osteoporosis in postmenopausal women. Clinical evidence suggests that raloxifene increases bone mineral density, decreases the risk of vertebral fractures, potentially prevents breast cancer, and has no significant effect on endometrial tissue growth. In addition, raloxifene has positive effects on LDL cholesterol and total cholesterol, although data on effects on cardiovascular morbidity and mortality are not yet available. Raloxifene may be used as an alternative to traditional hormone replacement therapy for osteoporosis, especially in women with a high risk of breast cancer. Raloxifene is an appropriate choice for women who cannot tolerate the adverse effects of estrogen or in women who decline estrogen therapy. However, raloxifene should not be used in women experiencing hot flashes as a primary symptom of estrogen deficiency or in those with a history of venous thromboembolism.

Each treatment decision should be based on the individual patient. Other agents (such as bisphosphonates and calcitonin) are available for women with osteoporosis who are primarily interested in bone-related benefits.

Ultimately, it will be information on cardiovascular or breast cancer benefits that will determine the future role of raloxifene. Trials assessing these possibilities are ongoing and should provide health care providers with more complete information on the advantages of raloxifene, if any, over standard hormone replacement therapy.

Conclusion

Raloxifene is an alternative to traditional hormone replacement therapy for the prevention and treatment of osteoporosis in selected postmenopausal women. More study is needed to verify possible benefits related to heart disease and breast cancer.

References

1. Boss SM, Huster WJ, Neild J et al. Effects of raloxifene hydrochloride on the endometrium of postmenopausal women. *Am J Obstet Gynecol.* 1997; 177:1458-64.
2. Delmas PD, Bjarnason NH, Mitlak BH et al. Effects of raloxifene on bone mineral density, serum cholesterol concentrations, and uterine endometrium in postmenopausal women. *N Engl J Med.* 1997; 337: 1641-7.
3. Kauffman RF, Bryant HU. Selective estrogen receptor modulators. *Drug News Perspect.* 1995; 8:531-9.
4. Friedl A, Jordan VC. What do we know and what don't we know about tamoxifen in the human uterus. *Breast Cancer Res Treat.* 1994; 31:27-39.
5. Baker VL, Jaffe RB. Clinical uses of antiestrogens. *Obstet Gynecol Surv.* 1996; 51:45-59.
6. Grese TA, Sluka JP, Bryant HU et al. Molecular determinants of tissue selectivity in estrogen receptor modulators. *Proc Natl Acad Sci U S A.* 1997; 94:14105-10.
7. McDonnell DP, Clemm DL, Hermann T et al. Analysis of estrogen receptor function in vitro reveals three distinct classes of antiestrogens. *Mol Endocrinol.* 1995; 9:659-69.
8. Brzozowski AM, Pike AC, Dauter Z et al. Molecular basis of agonism and antagonism in the oestrogen receptor. *Nature.* 1997; 389:753-8.
9. Webb P, Lopez GN, Uht RM et al. Tamoxifen activation of the estrogen receptor/AP-1 pathway: potential origin for the cell-specific estrogen-like effects of antiestrogens. *Mol Endocrinol.* 1995; 9:443-56.
10. Kuiper GG, Enmark E, Pelto-Huikko M et al. Cloning of a novel estrogen receptor expressed in rat prostate and ovary. *Proc Natl Acad Sci U S A.* 1996; 93:5925-30.
11. Mosselman S, Polman J, Dijkema R. ERb: identification and characterization of a novel human estrogen receptor. *FEBS Lett.* 1996; 392:49-53.
12. Paech K, Webb P, Kuiper GG et al. Differential ligand activation of estrogen receptors ERa and ERb at AP1 sites. *Science.* 1997; 277:1508-10.
13. Weiss DJ, Gurpide E. Non-genomic effects of estrogens and antiestrogens. *J Steroid Biochem.* 1988; 31:671-6.
14. Halachmi S, Marden E, Martin G et al. Estrogen receptor-associated proteins: possible mediators of hormone-induced transcription. *Science.* 1994; 264:1455-8.
15. Elgort MG, Zou A, Marschke KB et al. Estrogen and estrogen receptor antagonists stimulate transcription from the human retinoic acid receptor-a1 promoter via a novel sequence. *Mol Endocrinol.* 1996; 10:477-87.
16. Evista (raloxifene hydrochloride) package insert. Indianapolis, IN: Lilly; 1998.
17. Knadler MP, Lantz RJ, Gillespie TA et al. The disposition and metabolism of 14C-labeled raloxifene in humans. *Pharm Res.* 1995; 12(suppl):372. Abstract.
18. Ni L, Allerheiligen SRB, Basson R et al. Pharmacokinetics of raloxifene in men and postmenopausal women volunteers. *Pharm Res.* 1996; 13(suppl):430. Abstract.
19. Allerheiligen S, Geiser J, Knadler M et al. Raloxifene pharmacokinetics and the associated endocrine effects in premenopausal females treated during the follicular, ovulatory, and luteal phases of the menstrual cycle. *Pharm Res.* 1996; 13(suppl):430. Abstract.
20. Draper MW, Flowers DE, Huster WJ et al. A controlled trial of raloxifene (LY139481) HCl: impact on bone turnover and serum lipid profile in healthy postmenopausal women. *J Bone Miner Res.* 1996; 11:835-42.
21. Heaney RP, Draper MW. Raloxifene and estrogen: comparative bone-remodeling kinetics. *J Clin Endocrinol Metab.* 1997; 82: 3425-9.
22. Lufkin EG, Whitaker MD, Nickelsen T et al. Treatment of established postmenopausal osteoporosis with raloxifene: a randomized trial. *J Bone Miner Res.* 1998; 13:1747-54.
23. Ettinger B, Black DM, Mitlak BH et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene. Results from a 3-year randomized clinical trial. *JAMA.* 1999; 282: 637-45.
24. Buzdar AU, Marcus C, Holmes F et al. Phase II evaluation of Ly156758 in metastatic breast cancer. *Oncology.* 1988; 45:344-5.
25. Cummings SR, Eckert S, Krueger KA et al. The effect of raloxifene on risk of breast cancer in postmenopausal women. *JAMA.* 1999; 281:2189-97.
26. Walsh BW, Kuller LH, Wild RA et al. Effects of raloxifene on serum lipids and coagulation factors in healthy postmenopausal women. *JAMA.* 1998; 279:1445-51.
27. Grey AB, Stapleton JP, Evans MC et al. The effect of the anti-estrogen tamoxifen in cardiovascular risk factors in normal postmenopausal women. *J Clin Endocrinol Metab.* 1995; 80:3191-5.

Continuing Education

Raloxifene hydrochloride

Article 204-000-00-012-H01 (see page 1669)
Qualifies for 1.0 hour of CE credit

Learning objectives

After studying this article, the reader should be able to

1. Describe the chemistry, pharmacology, and pharmacokinetics of raloxifene.
2. Discuss clinical trials of raloxifene.
3. Describe the adverse effects and drug interactions of raloxifene.
4. Review the dosage, administration, and role of raloxifene therapy.
5. Summarize the information that should be provided to patients who are prescribed raloxifene.

Self-assessment questions

For each question there is only one best answer.

1. Raloxifene
   a. Is a first-generation selective estrogen-receptor modulator (SERM).
   b. Is a second-generation SERM.
   c. Demonstrates partial estrogen agonist activity in the uterus.
   d. Demonstrates partial estrogen agonist activity in breast tissue.
2. The absolute bioavailability of raloxifene is
   a. 2%.
   b. 10%.
   c. 50%.
   d. 60%.
3. Lactating and pregnant women should not take raloxifene.
   a. True.
   b. False.
4. Clinical studies indicate that raloxifene has what effect on markers of bone turnover?
   a. Increases markers.
   b. Decreases markers.
   c. No effect.
   d. Results are inconclusive at this time.
5. Raloxifene has been found to
   a. Decrease lipoprotein (a) levels to a greater degree than estrogen does.
   b. Decrease high-density-lipoprotein (HDL) cholesterol.
   c. Increase HDL cholesterol.
   d. Decrease total cholesterol and low-density-lipoprotein cholesterol.
6. Which of the following is true of the effect of raloxifene on endometrial proliferation?
   a. There are no significant effects.
   b. Endometrial proliferation increases.
   c. Endometrial proliferation increases to a greater extent than with estrogen.
   d. Endometrial proliferation increases to a greater extent than with tamoxifen.
7. Additional monitoring of raloxifene therapy is recommended for patients with
   a. Renal impairment.
   b. Hepatic impairment.
   c. Pregnancy.
   d. Vertebral fractures.
8. The most serious adverse effect associated with raloxifene therapy is
   a. Hot flashes.
   b. Breast cancer.
   c. Venous thromboembolism.
   d. Vaginal bleeding.
9. Which of the following is a common adverse effect of raloxifene?
   a. Nausea.
   b. Leg cramps.
   c. Rash.
   d. Diarrhea.
10. Extra caution is required when using raloxifene with all of the following drugs *except*
    a. Indomethacin.
    b. Ibuprofen.
    c. Tamoxifen.
    d. Diazepam.
11. Raloxifene therapy is appropriate for
    a. Women with a high risk of breast cancer.
    b. Women in whom the primary symptom of estrogen deficiency is hot flashes.
    c. Women with a history of venous thromboembolism.
    d. All postmenopausal women.
12. Raloxifene should be taken with meals.
    a. True.
    b. False.
13. Patients taking raloxifene should be counseled that raloxifene will help meet their calcium and vitamin D needs.
    a. True.
    b. False.
14. The recommended dosage of raloxifene is
    a. 35 mg/day.
    b. 50 mg/day.
    c. 60 mg/day.
    d. 65 mg/day.

15. Raloxifene recipients who are preparing for surgery should be counseled to do which of the following?
    a. Continue their raloxifene therapy as usual.
    b. Discontinue raloxifene if the surgery will require a recovery period of over two weeks.
    c. Discontinue raloxifene immediately after surgery and resume it after the recovery period.
    d. Discontinue raloxifene 72 hours before surgery.

AJHP continuing-education request form

AJHP CE process

ASHP members can now receive free continuing-education (CE) credit. Effective January 1, 1999, ASHP discontinued the $5 member test-grading fee for CE articles published in *AJHP*. (The fee for nonmembers is $10 per article.) The process for obtaining CE credit for articles has also been streamlined. The CE request form will accompany each CE article in *AJHP*, both in print and online (http://www.ashp.org). ASHP members can read the printed or online article, complete the CE request form, and send it to ASHP via mail, fax, or the Internet. If the test is submitted online, the member will receive a score and a CE certificate immediately. (Online journal CE is not currently available to nonmembers.) Readers without Internet access can receive copies of previously published *AJHP* CE articles by mail. A list of these articles, with an order form, is available through ASHP's Fax-on-Demand service (301-664-8888); ask for document 264.

Article: **Raloxifene hydrochloride**

ACPE #: 204-000-00-012-H01
CE credit: 1.0 hour

Expiration date: September 15, 2003

Instructions

1. Complete the application.
2. Record your responses on the answer sheet by darkening the box for the correct answer to each test question. (*Note:* The passing score is 70%.)
3. Complete the evaluation questions.
4. If not an ASHP member, choose your method of paying the $10 fee.
5. Choose the most convenient option to send your form (and payment, if applicable).

Mail: ASHP Customer Service Dept.
7272 Wisconsin Avenue
Bethesda, MD 20814

Fax: 800-665-ASHP(2747)

Online: CE tests can be submitted online (for members only) at http://ce.ashp.org.

Within two weeks of receiving your mailed or faxed form, ASHP will mail you a certificate of continuing pharmaceutical education or notify you that you did not achieve a passing score. Failed tests may be retaken one time at no additional cost. There are no refunds for failed tests. If you take the test online and do not pass, you may take it a second time online.

Questions? Call ASHP Customer Service at 301-657-4383.

The American Society of Health-System Pharmacists is approved by the American Council on Pharmaceutical Education as a provider of continuing pharmaceutical education.

Application

Name _____

ASHP member # _____

Address _____

City _____ State _____ Zip _____

Phone _____ Fax _____

Payment (for non-ASHP members only)

☐ Check payable to ASHP for $10 is enclosed.

Charge $10 to ☐ MasterCard ☐ Discover ☐ VISA ☐ American Express

Account # _____

Exp. date _____ Signature _____

☐ Purchase order # _____ attached

Evaluation

Your feedback will help us plan future CE articles. Please circle the number that best indicates your response to each statement below.

		Strongly Agree	Agree	Disagree	Strongly Disagree
		1	2	3	4
1.	The article's topic is relevant to my practice.	1	2	3	4
2.	I felt that I met the learning objectives.	1	2	3	4
3.	I can apply to my job something that I learned from this article.	1	2	3	4
4.	I learned something new.	1	2	3	4
5.	The article was easy to follow.	1	2	3	4
6.	I would like to see more educational programs on this topic.	1	2	3	4
7.	The test is fair.	1	2	3	4

8. Comments about this article/test: _____

9. Suggestions for other CE articles: _____

10. How long did it take you (in hours and minutes) to complete this article and test? _____

Raloxifene hydrochloride

ACPE # 204-000-00-012-H01

Answer Sheet

September 15, 2000, *AJHP*

ACPE 204-000-00-012-H01

1.0 hour

Darken the boxes corresponding to the correct answers.

	a	b	c	d
1.	☐	☐	☐	☐
2.	☐	☐	☐	☐
3.	☐	☐		
4.	☐	☐	☐	☐
5.	☐	☐	☐	☐
6.	☐	☐	☐	☐
7.	☐	☐	☐	☐
8.	☐	☐	☐	☐

	a	b	c	d
9.	☐	☐	☐	☐
10.	☐	☐	☐	☐
11.	☐	☐	☐	☐
12.	☐	☐		
13.	☐	☐		
14.	☐	☐	☐	☐
15.	☐	☐	☐	☐

5

Hospital Pharmacy
Volume 33, Number 8, pp 999-1005
1998 Lippincott Williams & Wilkins

NEW AND UNUSUAL DRUG USES

Estrogen for Uremic Bleeding

Jennifer Malinowski, PharmD and Jennifer Morales, BS Pharm†*

Practicing clinicians come across uses of pharmacologic agents that may not always be listed in the usual references. For example, glycerin injection for nerve block, H_2 antagonists in colorectal cancer, or colchicine for systemic sclerosis may represent novel, hard-to-find clinical applications. If you have encountered a new and/or unusual use of a drug, submit the information to this Hospital Pharmacy *feature. Send three copies, double-spaced, 1,000 word or less, to: Thomas G. Burnakis, PharmD, Baptist Medical Center, 800 Prudential Drive, Jacksonville, FL 32207. Please include a list of "key words" that an individual might logically look for in an index when searching for this information.*

*Assistant Professor of Pharmacy Practice, Wilkes University School of Pharmacy, Wilkes Barre, PA 18766; e-mail: malinows@wilkes.edu; † Pharmacy Department, The Cooper Health System, Camden, NJ

Our pharmacy received an order for 0.6 mg per kg intravenous conjugated estrogen for 5 days. Many of us were not familiar with this dosing regimen. We therefore contacted the physician, who informed us that the prescription was for the management of bleeding induced by uremia. This prompted us to research the use of estrogen for uremic bleeding in terms of mechanism of action, adverse effects, and efficacy.

MECHANISM OF BLEEDING IN PATIENTS WITH RENAL FAILURE

Although multiple factors have been implicated as potential inducers of bleeding episodes in patients with uremia, the exact pathophysiology is unknown. Several biochemical deviations have been identified that suggest defective platelet aggregation. Compounds that stimulate platelet aggregation, such as ADP and serotonin, have reduced concentrations in patients with renal failure. Concentrations of substances that inhibit platelet aggregation, such as cAMP and prostaglandin, are increased.[1,2]

NEW AND UNUSUAL DRUG USES INDEX

Hospital Pharmacy
Volume 33, Number 8, pp 999-1005
1998 Lippincott Williams & Wilkins

NEW AND UNUSUAL DRUG USES

Aug 1998

Estrogen for Uremic Bleeding

Jennifer Malinowski, PharmD and Jennifer Morales, BS Pharm†*

Practicing clinicians come across uses of pharmacologic agents that may not always be listed in the usual references. For example, glycerin injection for nerve block, H_2 antagonists in colorectal cancer, or colchicine for systemic sclerosis may represent novel, hard-to-find clinical applications. If you have encountered a new and/or unusual use of a drug, submit the information to this Hospital Pharmacy *feature. Send three copies, double-spaced, 1,000 word or less, to: Thomas G. Burnakis, PharmD, Baptist Medical Center, 800 Prudential Drive, Jacksonville, FL 32207. Please include a list of "key words" that an individual might logically look for in an index when searching for this information.*

*Assistant Professor of Pharmacy Practice, Wilkes University School of Pharmacy, Wilkes Barre, PA 18766; e-mail: malinows@wilkes.edu; † Pharmacy Department, The Cooper Health System, Camden, NJ

Our pharmacy received an order for 0.6 mg per kg intravenous conjugated estrogen for 5 days. Many of us were not familiar with this dosing regimen. We therefore contacted the physician, who informed us that the prescription was for the management of bleeding induced by uremia. This prompted us to research the use of estrogen for uremic bleeding in terms of mechanism of action, adverse effects, and efficacy.

MECHANISM OF BLEEDING IN PATIENTS WITH RENAL FAILURE

Although multiple factors have been implicated as potential inducers of bleeding episodes in patients with uremia, the exact pathophysiology is unknown. Several biochemical deviations have been identified that suggest defective platelet aggregation. Compounds that stimulate platelet aggregation, such as ADP and serotonin, have reduced concentrations in patients with renal failure. Concentrations of substances that inhibit platelet aggregation, such as cAMP and prostaglandin, are increased.[1,2]

NEW AND UNUSUAL DRUG USES INDEX

Additional factors, such as concomitant anticoagulant drugs and anemia of chronic renal failure, may also play a role.[2]

CLINICAL SIGNS AND SYMPTOMS

Hemostatic abnormalities are common in patients with advanced renal failure. Although fatalities do occur, the clinical symptoms and consequences that develop are usually mild and may include purpura, epistaxis, menorrhagia, and gastrointestinal bleeding.[3,4] The assumption that many of the manifestations associated with uremic bleeding are due to defective platelet functioning is supported by the prolonged bleeding times observed in these patients.

Bleeding time is a common and simple laboratory evaluation used to assess platelet functioning. The value is recorded in seconds and reflects the time required for bleeding to cease following a small puncture of the forearm. The average normal bleeding time is 4 to 5 minutes but can range from 2 to 9 minutes. Other laboratory measurements associated with abnormal hemostasis—such as prothrombin time, activated partial thromboplastin time, and platelet counts—are usually within normal limits.[5]

THERAPEUTIC APPROACHES TO UREMIC BLEEDING

Various mechanisms have been employed to reduce the incidence of bleeding in patients with uremic bleeding. Changes in dialysis regimen, such as using peritoneal dialysis rather than hemodialysis, using minimal or regional heparinization to reduce the risk of catheter occlusion, or omitting heparin completely during dialysis, have all had some success.[2]

However, these alterations achieve only a temporary reduction in prolonged bleeding times. Therefore, nondialysis therapies are also used for the prevention and treatment of bleeding in patients with renal failure.

Cryoprecipitate is a product derived from pooled human plasma and is rich in factor VIII, fibrinogen, and fibronectin. Infusion of cryoprecipitate reduces prolonged bleeding times and hemorrhage risk in uremic patients requiring surgery.[6] Disadvantages of cryoprecipitate infusions include variation in efficacy due to batch-to-batch differences in preparation and risks of blood-borne diseases such as hepatitis.[2]

Similarly, fresh frozen plasma (FFP), which also contains important coagulation factors, has been successful in correcting prolonged bleeding times in renal failure patients.[7] Like cryoprecipitate, FFP can have variations in efficacy, carries the risk of blood-borne diseases, and can cause allergic reactions.

The compound 1-deamino-8-d-arginine vasopressin (DDAVP), a synthetic antidiuretic hormone, increases factor VIII release and helps control bleeding in patients with coagulation disorders.[8] Intravenous, subcutaneous, and intranasal routes have been successful in shortening prolonged bleeding times in uremic patients at risk for bleeding.[8-12] Side effects of DDAVP include facial flushing, headache, nausea, pain at injection site, increased blood pressure, and hyponatremia.

In addition, cryoprecipitate, DDAVP, and FFP have only transient effects, necessitating repeated doses in patients requiring long-term therapy.

Erythropoietin has also been shown to decrease prolonged bleeding time and bleeding tendency in uremic patients.[13] Since a low hematocrit has been demonstrated to correlate positively with bleeding risk, the proposed mechanism involves an erythropoietin-induced increase in hematocrit.[14]

ESTROGEN IN UREMIC BLEEDING

The idea to use estrogen for uremic bleeding was stumbled upon during the treatment of female patients with von Willebrand's disease. In this hematologic disorder, defects in platelet aggregation put the patient at risk for bleeding. It was noticed that when women with the disorder became pregnant, their high estrogen levels reduced the tendency toward bleeding.[15] Therefore, clinicians postulated that supplementation with exogenous estrogen might bring about a similar reduced tendency in uremic patients.

In 1984, Liu et al reported on the use of estrogen in a patient with uremia, a prolonged bleeding time, and gastrointestinal bleeding without an identifiable lesion.[16] The subject was a 58-year-old male with endstage kidney disease who required frequent red blood cell transfusions. Following failed regimens of thrice weekly peritoneal dialysis treatments and multiple infusions of cryoprecipitates, 5 mg of conjugated estrogen (Premarin®) via an unspecified route was initiated.

After 9 consecutive days of therapy, the patient's bleeding time returned to normal and the gastrointestinal bleeding ceased. The patient was placed on a daily maintenance regimen of 2.5 mg Premarin. During a 12-month observation period, he had a normal bleeding time and no significant bleeding.

The success in this patient encouraged the authors to attempt estrogen therapy in an another six uremic patients with hemostatic abnormalities. In four of the patients, bleeding times became normal within 2 to 5 days, and in the remaining two the bleeding time was significantly shortened after 7 and 9 days of therapy, respectively.[16]

Since this study, at least seven other investigations have addressed the use of conjugated estrogen in uremic bleeding.[17-22] Although each study can be criticized on various methodological grounds, the repeated beneficial effect of the conjugated estrogen to reduce or normalize the bleeding time serves to confirm the efficacy of treatment.

Estrogen prescribed for patients with prolonged bleeding times (ranging between 7 and 30 minutes) achieved either normalization or at least a 50% reduction in bleeding time.[17-22] Although not definitively proven by direct comparative trials, estrogen therapy appears to work slower (in 6 to 24 hours) but last longer than cryoprecipitates, FFP, and DDAVP.

The correction of abnormal bleeding times was noticeable within 1 day in most patients and had an average peak effect after 3 to 9 days.[17-22] The duration of effect persisted for 3 to 25 days following completion of therapy and was dependent on the route of administration. The patients reverted to pretreatment bleeding times earlier after discontinuing oral estrogen (within 3 to 10 days) compared with patients assigned intravenous estrogen (15 to 25 days).[16,20]

More estrogen is required to achieve normalization of bleeding time than is traditionally prescribed to patients requiring estrogen replacement therapy for menopause, osteoporosis, or contraception. A common IV dose used for abnormal bleeding was 0.6 mg per kg of conjugated estrogen for 5 days. Initial oral doses used were variable and ranged from 5 to 50 mg of conjugated estrogen. One study by Bronner et al used combination therapy with norethynodrel 2.5 mg and mestranol 0.1 mg for bleeding gastrointestinal telangiectasis and also reported a positive outcome.[20] It would appear that the higher doses are more successful and that in patients with minimal response to low doses, higher doses often are beneficial.[19,20]

Patients in these studies did not develop severe adverse effects associated with estrogen therapy, even though higher doses were used.[17-22] Male patients enrolled into the study did not report any complaints associated with estrogen, such as breast tenderness, loss of libido, or impotence. In addition, no hot flashes, nausea, vomiting, or thromboembolic complications were observed. A word of caution is in order since the brief duration of therapy (range: 5 days to 1 year) and the small patient populations may have limited the expression of long-term side-effects.

The optimal route of administration, whether oral or parenteral, is unclear, and no studies have done a head-to-head comparison. Although both routes are effective, onset via the oral route is somewhat slower than the intravenous. On the other hand, the IV route is more expensive, carries the potential for infusion-related side-effects, and may require hospital admission to administer the drug.

It has been recommended that patients who have prolonged bleeding times with no severe bleeding be prescribed oral estrogen, while patients who develop severe bleeding be given IV estrogen.[21]

With prolonged therapy by either route, concerns over endometrial hyperplasia and either breast or endometrial cancer cannot be overlooked. In female patients with an intact uterus, it is prudent to also consider concomitant progestin. Whether this will affect overall efficacy of the estrogen on bleeding time is not certain. In the one study where combination therapy was used, there was resolution of the elevated bleeding time within 1 week.[20]

There is question over the place of estrogen in the treatment of uremic bleeding compared with more traditional modalities. Cryoprecipitate, FFP, and DDAVP are all better-established therapies. Furthermore, the increasing use of erythropoietin in patients with renal failure may help resolve some hemostatic defects in uremia. However, each of these treatments has its drawbacks.

Both cryoprecipitate and FFP have the potential to transmit infectious disease and precipitate allergic reactions.[7] The use of DDAVP, though less risky, is mediated by the development of tachyphylaxis with repeated use.[3] Erythropoietin helps correct the bleeding disorders in uremia, probably related to its effects to increase hematocrit.[13,14] Yet, if the underlying problem is one of altered platelet function, simply increasing the number of platelets may not offer a full correction. Lastly, none of these other therapies offer the option of oral dosing, and all are considerably more expensive than estrogen.

CONCLUSIONS

The role of estrogen for uremic bleeding is unclear. It appears that estrogen offers an alternative to patients who do not respond to or are intolerant of cryoprecipitate and DDAVP. A reasonable option for patients with severe bleeding unresponsive to other available therapies is 0.6 mg per kg intravenously until bleeding stops. Initial oral doses ranging from 5 to 50 mg daily are acceptable for patients requiring less urgent correction and for maintenance therapy.

Information on long-term therapy with high-dose conjugated estrogen is not available. Risks versus benefits should be weighed when considering high doses of estrogen for extended periods of time.

Although warranted, it is uncertain if large, well-designed trials of estrogen in uremic bleeding will be

conducted. It is more likely that estrogen will continue to be used by clinicians as an option for, or addition to, other agents in the armamentarium.

Some follow-up about the patient whose treatment stimulated this discussion is in order. As it turns out, she received dual therapy with IV estrogen and DDAVP, to which she responded immediately. Her bleeding time decreased to 5.5 minutes from a baseline of 12 minutes within 24 hours. Both medications were discontinued after two doses, and the patient was discharged on neither estrogen nor DDAVP.

The patient remains on her thrice-weekly hemodialysis treatments with erythropoietin replacement and has had no repeat of the prolonged bleeding time. Unfortunately, since estrogen and DDAVP were begun and discontinued at the same time, it is difficult to determine what part either therapy played in reducing the patient's bleeding time.

REFERENCES

1. Eknoyan G, Wacksman S, Glueck H, et al. Biochemical abnormalities of platelets in renal failure: Evidence for decreased platelet serotonin, adenosine diphosphate, and magnesium-dependent adenosine triphosphate. *Am J Nephrol.* 1981; 1:17-23.

2. Lohr J, Schwab S. Minimizing hemorrhagic complications in dialysis patients. *J Am Soc Nephrol.* 1991;2:961-275.

3. Remuzzi, G. Bleeding in renal failure. *Lancet.* 1988;1:1205-1208.

4. George J, Shattil S. The clinical importance of acquired abnormalities of platelet function. *N Engl J Med.* 1991;324(1):27-39.

5. Larson, SO. On coagulation and fibrinolysis in renal failure. *Scand J Haematol.* 1971;15(suppl):1-59.

6. Janson PA, Jubelirer SJ, Weinstein MJ, et al. Treatment of the bleeding tendency in uremia with cryoprecipitate. *N Engl J Med.* 1980;303:1318-1322.

7. Boyd GL, Diethelm AG, Gelman S, et al. Correcting prolonged bleeding during renal transplantation with estrogen or plasma. *Arch Surg.* 1996;131:160-165.

8. Mannucci PM, Pareti FF, Ruggeri ZM, et al. 1-deamino-8-d-arginine vasopressin: A new pharmacologic approach to the management of hemophilia and von Willebrand's disease. *Lancet.* 1977;1:869-872.

9. Watson AJS, Keogh JB. Effect of 1-deamino-8-d-arginine vasopressin on the prolonged bleeding time in chronic renal failure. *Nephron.* 1982;32:49-52.

10. Mannucci, PM, Remuzzi, G., Pusineri, F et al. Deamino-8-d-arginine vasopressin shortens the bleeding time in uremia. *N Engl J Med.* 1983; 308:8-12.

11. Vigano GL, Mannucci PM, Lattuada, A. et al. Subcutaneous desmopressin (ddavp) shortens the bleeding time in uremia. *Am J Hematol.* 1989; 31:32-35.

12. Shapiro MD, Kelleher SP. 1-deamino-8-d-arginine vasopressin shortens the bleeding time in uremia. *Am J Nephrol.* 1984;4:260-261.

13. Huralb S, Al-Momen AK, Gader AMA, et al. Effect of recombinant human erythropoeitin (rhEpo) on the hemostatic system in chronic hemodialysis patients. *Clin Nephrol.* 1991;36:252-257.

14. Fernandez F, Goudable C, Sie P, et al. Low hematocrit and prolonged bleeding time in uraemic patients: Effect of red blood cell tranfusions. *Br J Haematol.* 1985;59:139-148.

15. Leone G, Monet E, Paparatti G, et al. Von Willebrand's disease in pregnancy. *N Engl J Med.* 1975;293:456.

16. Liu Y, Kosfeld R, Marcum S. Treatment of uremic bleeding with conjugated estrogen. *Lancet.* 1984;2:887-890.

17. Livio M, Mannucci PM, Viagno G, et al. Conjugated estrogens for the management of bleeding associated with renal failure. *N Engl J Med.* 1986 315:731-735.

18. Greger B, Bockhorn H, Reeb A, et al. Treatment of perioperative bleeding after kidney transplant by conjugated estrogen. *Transplant Proc.* 1987;19:3704-3706

19. Vigano G, Gaspari F, Locatelli M, et al. Dose-effect and pharmacokinetics of estrogens given to correct bleeding time in uremia. *Kidney Int.* 1988;34:853-858.

20. Bronner MH, Pate MB, Cunningham JT, et al. Estrogen progesterone therapy for bleeding gastrointestinal telangiectasias in chronic renal failure. *Ann Intern Med.* 1986;105:371-374.

21. Heistinger M, Stockenhuber F, Schneider B, et al. Effect of conjugated estrogens on platelet function and prostacyclin generation in CRF. *Kidney Int.* 1990;38:1181-1186.

22. Shemin D, Elnour M, Amaramtes, et al. Oral estrogens decrease bleeding time and improve clinical bleeding in patients with renal failure. *Am J Med.* 1990:89:436-440.

23. St. Peter W, Mihalovic S, Vargas-Ruiz M, et al. Chronic renal failure and end stage renal disease. In: Dipiro J, Talbert R, Yee G, et al, eds. *Pharmacotherapy: A Pathophysiologic Approach.* 3rd edition. Stamford, CT: Appleton and Lange; 1997.