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Raloxifene; an Agent for Grandam- A Review

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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 32.5 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.

KEYWORDS; Breast neoplasms; Dosage; Estrogen agonist-antagonists; Mechanism of action; Metabolism; Osteoporosis; Pharmacokinetics; Raloxifene hydrochloride; Toxicity.

I. INTRODUCTION;

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 Raloxifene hydrochloride 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 nonsteroidal derivative that binds to the estrogen receptor.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.

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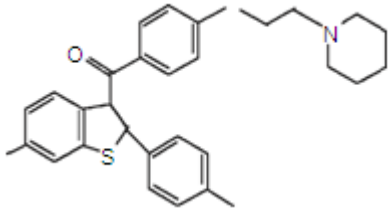

Figure 1. Chemical structure of raloxifene

Biological activity;

Raloxifene (brand name: Evista) is used to prevent and treat osteoporosis in women who undergo menopause. It is a selective estrogen receptor modulator (SERM).

Mechanisms of action;

There are three interactive mechanism that explain the pharmacology of SERMs: Differential estrogen-receptor expression in a given target tissue, differential estrogenreceptor conformation on ligand binding and differential expression and binding to the estrogen-receptor of coregulator proteins. There are two main types of estrogen receptors α and β. The α-receptor is mainly an activator and β-receptor inhibitor. The SERMs bind to both receptors, functioning as pure antagonist when binding to β-receptors and as a partial agonist when binding to the α-receptor. The different action of the individual SERM depends on coregulatory proteins and their ability to recruit coactivators. Estrogenic activation inhibits osteoclasts and thereby reduces the bone resorption by osteoclasts that restores the balance between bone formation and bone resorption.

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.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. 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. 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 17βestradiol, 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.For example, the estrogen receptor contains two transcriptional activation functions, AF-1 and AF-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.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. Estrogens and SERMs affect each of these receptors differently.For example, with estrogen-receptor α, 17β-estradiol activates transcription, 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)

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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.The extent to which each tissue expresses these receptor subtypes in humans is currently unknown.

Pharmacokinetics

The pharmacokinetics of raloxifene were investigated in over 1500 women in clinical trials.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 a maximum plasma concentration.

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. 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.Raloxifene and its conjugates are 95% bound to albumin and α1 -acid glycoprotein in vitro. Raloxifene does not bind to sex steroid-binding globulin. 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. Conjugate formation includes raloxifene 4′-glucuronide, 6-glucuronide, and 6,4′-diglucuronide. Very small amounts of free raloxifene are detected in the circulation.

other metabolites suggests that raloxifene is not metabolized by the cytochrome P-450 isoenzyme system. 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. 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. The half-life (t ½) of raloxifene at steady state ranges from 15.8 to 86.6 hours and averages 32.5 hours. 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.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 conjugate.

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.

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,

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respectively. The frequencies of breast tenderness and vaginal bleeding did not differ significantly from those for placebo.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.

Drug Interaction;

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 raoxifene should be avoided.

Effects of raloxifene on bone;

Raloxifene decreases the markers of bone turnover by 30%–40% after 1 year and increases bone density at several scanning sites by 2%–3% after 3 years in postmenopausal women with osteoporosis. Raloxifene decreases the incidence of vertebral fractures by 30%–50% (Figure 2) but does not decrease the incidence of hip fractures or other nonvertebral fractures.By contrast, estrogen reduces vertebral and hip fractures rate by 34% over average of 5.2 years of therapy. Studies that have looked at bone mineral density (BMD), bone architecture and bone turnover suggest that estrogen is more effective antiresorptive agent than raloxifene. Raloxifene increases BMD at the hip but studies have not shown decrease in any non-vertebral fracture. Bisphosphonate therapy decreases vertebral fractures by 48% only slightly more than raloxifene therapy does and decreases hip fracture incidence by 30 to 40% in postmeanopausal women.

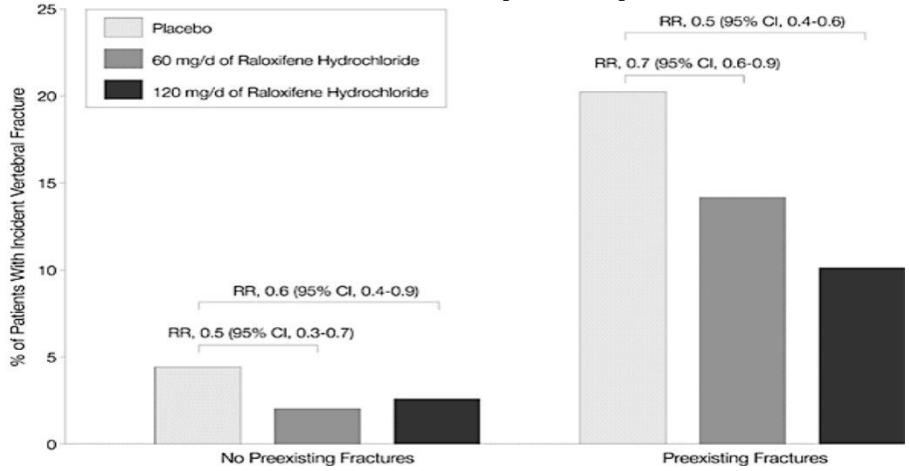

Figure-2; Effects of raloxifene on bone

Effects on the genitourinary tract;

Raloxifene does not stimulate the growth of the endometrium nor the vaginal mucosa. Therefore raloxifene would not be useful for either treating postmenopausal estrogen deficiency symptoms of the lower urinary tract or vagina-like dyspareunia, frequency of urination, urinary tract infections, or urinary incontinence. Tamoxifen as estrogen has been related to endometrial cancer (2.5-fold increase). The STAR P-2 trial demonstrated increased incidence of endometrial cancer in the tamoxifen group compared with raloxifene but without statistical significance.

Effects on cardiovascular risk factors;

Raloxifene favorably alters biochemical markers of cardiovascular risk by decreasing LDL-cholesterol, fi brinogen, and lipoprotein, and by increasing HDL2-cholesterol without raising triglycerides. In contrast to hormone replacement therapy, raloxifene has no effect on HDL-cholesterol and PAI-1 and a lesser effect on HDL2-cholesterol and lipoprotein. Do these favorable

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biochemical effects mean protection against cardiovascular disease? In a secondary analysis of the MORE trial, with women with increased risk of cardiovascular risk, cardiovascular events were signifi cantly reduced. These results were not confi rmed in the RUTH trial where postmenopausal women at risk for cardiovascular diseases were randomized to raloxifene versus placebo. Raloxifene was neither associated with increased nor decreased cardiovascular event. Considering death rates in the RUTH trial, there was a slight signifi cant increase of fatal strokes (but not stroke overall) in the raloxifene group which was offset by a significant decrease in non-cancer and non-cardiovascular deaths in the raloxifene group. While these results are not necessarily true it is wise to consider high risk of stroke a relative contraindication to raloxifene therapy. On the other hand, the presence of ischemic heart disease is neither an indication nor a contraindication for raloxifene therapy.

Reduction of risk of breast cancer

When choosing an agent for treatment of any health problems, other effects have to be taken into consideration. The secondary benefit of raloxifene is prevention of hormone positive breast cancer. There are no current guidelines on primary prevention of breast cancer so raloxifene for that use is not at present indicated for that use. The yearly overall risk of newly diagnosed breast cancer is one in 500 for a 70-year-old woman and 1 in 400 for an 80-year-old woman, that would be approximately 1 in 40–50 over 10 years and 1 in 20–25 over 20 years. The fact that while breast cancer comprises 20% of mortality for younger women, other disease such as cardiovascular diseases can be attributed to a majority of deaths for older women and breast cancer only to a small percentage.

Increase in risk of thromboembolic events

The increased incidence of venous thromboembolism is the main concern of raloxifene therapy and previous history of venous thromboembolism is a contraindication for use of raloxifene. Old age is risk factors for thromboembolic events reaching approximately 0.5% a year at the age of 80. Raloxifene treatment increases the risk 1.5–3.0 times which would mean absolute risk of 0.75%–1.5% a year. Over 5 years that could mean 3%–7% risk and over 10 years of therapy up to possibly 15% likelihood of a thrombosis. Other risk factors are obesity, tendency for thrombosis, cancers, inflammatory diseases, and surgery. Hospital stay with immobility, stroke, heart failure, respiratory failure, sepsis or inflammation, increase the risk considerably. It is wise to use active thromboprophylaxis and stop raloxifene treatment during the hospital stay until the patient is fully mobile for these conditions.

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.

II. CONCLUSION

The decisions to treat osteoporosis for fracture prevention needs to be discussed with the individual and the fracture risk needs to be taken into account along with other benefits and risks of treatment. Every older individual should be advised upon adequate calcium and vitamin D replacement. Individuals at increased risk of fracture either because of osteopenia or osteoporosis should be evaluated for further treatment. Raloxifene is an effective treatment for prevention of vertebral fractures in postmenopausal women. Raloxifene has the added benefit of prevention hormone positive breast cancer but increases risk of venous thromboembolism. Raloxifene could be used as

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

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