Women's Health: Osteoporosis

Osteoporosis: Regulatory View

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Synopsis

Evaluation of drugs proposed for the prevention and treatment of osteoporosis is difficult. The Food and Drug Administration (FDA) has issued guidelines for the clinical investigation of drugs in this class.

Estrogen has been approved for the treatment of postmenopausal osteoporosis. Administration of estrogen requires careful assessment of the risks and benefits for the individual patient. The smallest effective dose should be used. There are both potential risks and benefits for the concommitant administration of a progestin.

Calcitonin has also been approved; however, the need for parenteral administration, the problem of antibody formation, and expense may limit the usefulness of the currently marketed preparations.

Calcium has been recommended, but because it is considered a food supplement it has not been submitted to FDA for evaluation of its safety and efficacy as a drug in the treatment of osteoporosis.

Other drugs under investigation include anabolic steroids, fluorides, vitamin D substances, biphosphonates, parathyroid hormone, and thiazides.

EVALUATION OF DRUGS used in the treatment of osteoporosis is difficult. Osteoporosis is a chronic disease with a long period of latent deterioration before symptoms in the form of pain and fractures appear. The progression of osteoporosis is not stopped quickly or with dramatic effect. A number of factors contribute to the difficulty of evaluation.

Establishing the diagnosis in the early state and following the progression of this disease are difficult. Standard X-rays of the bone are very insensitive measures, capable of detecting only large losses of 30 or 40 percent of bone mass.

Clinicians who study osteoporosis must utilize techniques that will assess both cortical and trabecular bone. These tests are described in guidelines for clinical testing that are available from the Food and Drug Administration (FDA) (*1*). These guidelines describe the various laboratory techniques used in evaluation and make suggestions for the implementation of clinical trials. A major consideration in the use of these various tests is to differentiate the effects of treatment on the hard, plate-like cortical bone from the spongy trabecular bone. Improvement in one type of bone may be accompanied by no change or even deterioration in the other. Therefore, it is important to assess both types.

Carefully controlled studies are necessary to ascertain whether the drug or spontaneous variation is causing changes or improvements. The time course of treatment response is also important. For example, in treatment with calcitonin, early response may not be sustained, and refractoriness to treatment may develop in 1-2 years.

Another consideration is the effect of treatment on the quality of bone. For example, fluoride may induce, particularly in the early stages of treatment, a brittle type of bone, which may be more vulnerable to fracture. Later in the treatment course, the quality of this newly formed bone tends to improve (*2*).

Bones are not static tissues; although they appear to be adynamic because of their physical solidity, they are undergoing constant remodeling due to the activity of osteoclasts that break down bone and osteoblasts that build up bone. The degree and speed of this remodeling activity, which may vary considerably in patients with osteoporosis, may be important in determining response to the various types of treatment.

Different drugs will affect the remodeling process in varying ways. A patient with a high turnover of bone may be more affected by treatment than a patient whose bone is relatively quiescent (*3*). Phys-

iological interactions of naturally occurring hormones and vitamins in the body may be important. Seemingly paradoxical effects may be noted with substances known to cause breakdown of bone contributing to the building of bone through secondary effects. For example, parathyroid hormone will activate osteoclastic activity, but it will also stimulate the production of 1,25-dihydroxycholecalciferol ($1,25\text{-}(OH_2)D_3$) in the kidney, which will have a beneficial effect on calcium absorption (*4*).

Sampling errors of bone density and morphology must be considered. There may be different degrees of bone response in various locations of the skeleton. The age of the study population is also important. Early in menopause, fractures tend to occur in the wrists and vertebrae; later, hip fractures become increasingly frequent.

While laboratory measures of bone density and morphology are helpful, clinical response as determined by a reduction of fracture frequency is a more definitive measure of efficacy. Currently, our chief therapeutic approach to osteoporosis is in the area of prevention. We have very little evidence that once bone is lost we can restore it. For example, with estrogen therapy, if one wishes to have a significant impact in preventing bone loss in the postmenopausal period, one must treat within 6 years of the menopause (*5*).

Drugs Used in the Treatment of Osteoporosis

Estrogen is the foremost drug to be considered. Epidemiologic and interventional studies show that estrogens are important in maintaining bone structure. If functioning ovaries are removed surgically and estrogen is not replaced, bone will be rapidly lost. Retrospective studies indicate that fractures are less frequent in women who have taken estrogen after menopause. Although we have good evidence that estrogen is an effective agent, we do not know how it works because bone has no, or very few, estrogen receptors.

There is considerable evidence that estrogen may modify the effect of parathyroid hormone on bone resorption. When estrogens are given to patients with postmenopausal osteoporosis, the following changes are usually found: retention of calcium and phosphorus, a decrease in urinary hydroxyproline, and an increase in serum immunoreactive parathyroid hormone (*6*).

Estrogen may also stimulate the kidney to produce $1,25\text{-}(OH_2)D_3$, which helps to absorb calcium from the intestinal tract. Another effect of estrogen may be on the stimulation of calcitonin, which decreases bone breakdown.

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The overriding issue in estrogen therapy is safety. One must consider the cancer-promoting potential of estrogens. Estrogen given to postmenopausal women will increase the risk of endometrial cancer by a factor of 4–10 (*7*). The risk increases with the duration of use and the strength of the estrogen preparation. Some studies show that the risk for endometrial carcinoma drops rapidly after the termination of treatment. However, a recent study shows some persistence of risk for 10 years after stopping estrogen therapy (*8*). It has become common practice to administer another sex hormone, a progestin, for 10–13 days a month in conjunction with estrogen to prevent unrelieved stimulation of the endometrium. Excessive and unopposed stimulation of the endometrium by estrogen leads to endometrial hyperplasia, which seems to be a forerunner of malignancy (*9*).

There is fairly good evidence that endometrial hyperplasia is prevented by progestin therapy. However, it is not yet established that endometrial carcinoma will also be prevented. In addition, there are potential risks with the addition of a progestin to estrogen replacement regimens. Progestins may have an adverse effect on blood lipids (for example, the reduction of high density lipoprotein cholesterol) and also on carbohydrate metabolism, which may then increase the risk for disease of the heart and blood vessels. These adverse effects, if they do occur, probably will depend to a considerable degree on the type and quantity of progestin used.

The other important target organ of estrogen in regard to cancer-producing potential is the breast. Here the evidence for any effect is very mixed. The weight of the evidence shows that postmenopausal estrogen therapy is not associated with an increase in breast cancer (*10*).

Obviously, in women who have had a hysterectomy, the risk for endometrial carcinoma is

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absent. On the other hand, in women who have increased risk factors for cancers of endocrine-responsive organs, one must be very careful about giving estrogens. Similarly, a history of thromboembolic disease, such as blood clots to the lung, may militate against the use of estrogens. Thus, the decision of whether or not to give estrogen replacement therapy to the postmenopausal woman requires a very careful risk/benefit assessment.

On the benefit side of the assessment, one must consider those factors that will make a patient more vulnerable to osteoporosis. These factors include being white, thin, and of northwest European extraction, having a slender bone structure, and having delayed onset of menses or an early cessation of menses. Other adverse factors are smoking and excessive alcohol consumption (*11*).

In summary, there is good evidence that estrogen is a valuable agent for preventing the progression of osteoporosis, but clinical judgment is necessary to decide which patients should receive it. Also, it is important to use the smallest effective dose. Since it is impractical to titrate each patient because of the relative insensitivity of bone density measurements to detect changes over short periods of time, one must rely on the results of clinical investigations for guidance in choosing the smallest effective dose. In the case of conjugated estrogens, the smallest dose shown to retard bone loss is 0.625 mg/day. Doses smaller than this, e.g., 0.3 mg/day, do not seem to be effective. Larger doses incur an increase in the risk of adverse effects (*12*).

Other agents that have been accepted as useful in the treatment of osteoporosis include calcium and calcitonin.

Calcium is considered a food supplement and, as such, has not been subjected to the FDA drug approval process for determining its safety and efficacy in the treatment of osteoporosis. The beneficial effect of supplemental calcium has not been clearly demonstrated; it may be helpful only in women who have definitely inadequate dietary intakes. In any event, increasing the daily intake of calcium beyond 1500 mg does not seem to confer additional benefit and may carry with it an increasing risk of adverse effects, such as inducing kidney stones (*13*).

Calcitonin was approved several years ago by FDA. Like estrogen, it is a naturally occurring hormone. It is believed to act beneficially in osteoporosis by slowing the breakdown of bone by osteoclasts. It has several important disadvantages. Calcitonin is expensive and must be given daily by injection. It also may lose its effectiveness after 1-2 years. The currently available hormone (originally derived from salmon) has a structure somewhat different from the calcitonin secreted by humans. This difference in protein structure may lead to antibody formation and may be a factor in loss of effectiveness. Calcitonin with the identical composition of the substance produced in humans may soon be available. This product may have a more sustained effectiveness or may be useful in patients who have become refractory to the currently marketed (salmon) calcitonin (*14*).

Other drugs are under investigation with varying degrees of promise for the treatment of osteoporosis. Fluoride has a definite beneficial effect in stimulating trabecular bone growth; however, the quality of the bone that is induced may be suboptimal because of its brittleness. There are also side effects such as nausea and bone pain (*15*).

Anabolic steroids such as stanozolol show some preliminary evidence of benefit in osteoporosis. However, there are side effects such as liver toxicity, virilization, and adverse effects on blood cholesterol composition which may greatly limit their usefulness (*16*).

The biphosphonates are a class of drugs that act by depressing osteoclastic function and may be valuable in conjunction with other drugs in a form of treatment called "coherent therapy" or ADFR (activation, depression, free period, retreatment). In this therapy, the osteoclasts are first activated by drugs such as phosphates and parathyroid hormone. This initial phase of treatment stimulates a functioning osteoclast-osteoblast coupled unit. The osteoclastic portion of this unit is then depressed by a drug such as biphosphonate (e.g., etidronate); the osteoblasts then function unopposed. This approach holds promise in building bone, that is, restoration of bone tissues rather than merely preventing further loss (*17*).

Parathyroid hormone alone may be useful in certain circumstances. One of its potential benefits is the

stimulation of intestinal calcium absorption through its effects on vitamin D (*18*).

Thiazides have been used to retard urinary calcium loss (*19*).

In conclusion, at present the mainstays for drug therapy for postmenopausal osteoporosis are estrogen and perhaps calcium. These drugs act to retard further loss of bone structure and are to be considered primarily preventative in nature. Other therapies under investigation may offer additional benefits, particularly in the area of bone restoration.

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