Panel Session: Prevention/Treatment

Panel Summary

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THIS PANEL discussed various strategies that are available for the prevention and treatment of postmenopausal osteoporosis. Prevention, the ideal approach to osteoporosis, involves interventions that will retard or delay bone loss. Treatment of osteoporosis by use of agents to replace lost bone when bone loss has already occured is important in preventing new fractures. The four experts on this panel reviewed the benefits and risks of currently available preventive and therapeutic regimens used to maintain bone mass. They presented new investigational approaches that may hold promise for maintaining and restoring bone mass, and thus decrease the susceptibility of bone to fracture.

The first panelist, Dr. Elizabeth L. Barrett-Connor of the University of California at San Diego School of Medicine, presented an assessment of the benefits and risks of long-term use of estrogen to prevent or delay postmenopausal bone loss. The benefit of estrogen replacement therapy on bone mass in osteoporosis is well established. It is also associated with an increased risk of endometrial cancer. Less certain is the relationship between estrogen use and breast cancer. Data on the additional benefit of estrogen use on reducing the risk of cardiovascular disease, as well as how this positive effect may be negated by the addition of progestin to estrogen replacement therapy, were discussed.

It is generally accepted that a major risk of estrogen replacement therapy is an increased risk of endometrial cancer. Overall, studies have indicated that women treated with estrogen for 5 years or more have a five times greater risk of endometrial cancer. Data from 1980, however, showed that even when the incidence of endometrial cancer rose, the overall mortality rate in those women actually decreased (*1*). The addition of progestin reduces the risk of endometrial cancer, but may also negate the protective effect that estrogen therapy alone has on reducing heart disease because of progestin's adverse effect on blood lipids.

The overall consensus has been that estrogens do not increase the risk of breast cancer. The majority of the reported studies analyzed data from women who had treatment for less than 10 years. The issue of long-term risk of breast cancer is not completely settled as yet, in view of studies of women who took diethylstilbestrol; the data suggest an association between breast cancer and estrogen after 20 years of use.

Similarly, two other studies, a large case-control study published in the British Journal of Cancer in 1986 (*2*), and a case-control study published in JAMA in 1967 (*3*), showed that while the relative risk of breast cancer is low in women with less than 5 years of estrogen use, the risk increases after 20 years of use. Dr. Barrett-Connor pointed out that the women in these studies primarily were on prolonged estrogen therapy because of premature menopause, which may already be a risk factor for breast cancer. Until more conclusive evidence can be established, no definitive statement can be made about the risk of breast cancer resulting from prolonged estrogen use for the treatment of osteoporosis.

On the positive side, one of the great benefits of estrogen therapy may be its effect on reducing the risk of cardiovascular disease. Researchers have examined this association using case-control studies, a number of cohort studies, and data from the Lipid Research Clinics. Of the numerous case-control studies conducted, five showed a protective effect, two showed no effect, and one showed a greatly increased risk of cardiovascular disease with estrogen use. Of the numerous cohort studies that followed estrogen users over time, most have shown a low relative risk, except for an analysis of the data from the Framingham group, in which an increased risk was found. However, another analysis of the Framingham data, which used a different methodology for risk factor criteria, found a significantly reduced risk of heart disease. At this time, the majority of evidence suggests that estrogen use has a decidedly protective effect against cardiovascular disease.

Dr. Barrett-Connor pointed out that patients and physicians are faced with the dilemma of using estrogen alone to prevent osteoporosis, which increases the risk of endometrial cancer, or combining estro-

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gen and progestin to reduce this risk, but, in turn, possibly blunting the protective effect of estrogens on heart disease. These benefits and risks need to be evaluated further before arriving at definitive recommendations for treating osteoporotic women with hormone replacement therapy.

Dr. Robert Lindsay, Professor of Clinical Medicine at Columbia University in New York, discussed several therapies for the prevention of postmenopausal osteoporosis. Dr. Lindsay reviewed the efficacy of estrogen replacement in postmenopausal women, as well as several alternative measures, including the use of progestins, calcitonin, and diphosphonates.

Estrogen therapy prevents bone loss, and continues to do so as long as the therapy is provided. This effect is apparent regardless of the age at which treatment is started, but most studies indicated that the effects are more beneficial if the therapy is begun as early as possible in the menopause. Data from a cross-section of studies of estrogen use after 10 years show that estrogen prevents the loss of cortical and trabecular bone, and that bone mass in the vertebra and hip is preserved. While estrogen does not prevent all fractures, Dr. Lindsay reported that estrogen decreased the prevalence of vertebral fractures by 75 percent, and resulted in a decrease in hip fractures after 10 years of use.

The most common route of delivery for estrogen therapy is oral administration. However, other routes are being tested, such as injection, vaginal delivery, and use of a transdermal patch.

Most of the alternative strategies to estrogen replacement to prevent postmenopausal bone loss, as presented by Dr. Lindsay, pose unanswered questions that must be addressed before these therapies can be recommended for use. For example, as discussed in the previous presentation, the effects of long-term use of progestins, and their possible negative effect on reducing cardiovascular disease, have not been fully studied.

Another compound that holds promise for preventing bone loss is calcitonin, although data on its use are limited. Calcitonin is an inhibitor of osteoclast bone resorption. It has also been used in the treatment of Paget's disease of the bone. There are no long-term data on the evaluation of calcitonin in preventing the acceleration of bone loss in postmenopausal women. In addition, the main route of administration of calcitonin is by injection, which has little appeal to an asymptomatic patient. The recent development of intranasal calcitonin may make the drug more acceptable. More data are needed on its bioavailabililty by alternative routes of administration, as well as on the efficacy and safety of calcitonin in preventing bone loss in osteoporosis. Other agents used in the treatment of Paget's disease, such as the diphosphonates, are being evaluated for their effectiveness in preventing bone loss in postmenopausal women.

Dr. Lindsay concluded that estrogen therapy continues to be the major agent for the prevention of osteoporosis in postmenopausal women. Alternative therapies are being studied; however, data on the safety and effectiveness of these potential candidates are not adequate at this time.

Dr. Morris Notelovitz, Founder/Director of the Center for Climacteric Studies and the Climacteric Clinic in Gainesville, FL, reviewed the use of hormonal therapy in terms of both its socioeconomic impact and factors that affect compliance. He presented physiological and psychological effects of hormonal therapy on the "total" woman, and which factors are more likely to promote compliance with replacement therapy. Dr. Notelovitz discussed both the short-term and the long-term benefits of estrogen therapy.

In 1984, nearly half the women between the ages of 35 and 65 were in the labor force. Many factors will impact on the productivity and quality of life of this age group; one of these is hormonal therapy. A highly desired benefit of estrogen replacement therapy, the prevention of bone loss, was discussed and affirmed. In addition, Dr. Notelovitz described several studies of the positive effect hormonal therapy can have on factors that may affect performance; these include the discomforts of menopause, vasomotor incidences (hot flashes), atrophic vaginitis, and waking episodes during sleep.

To benefit from the positive influences of hormonal therapy, physicians need to convince the patient that the benefits of estrogen therapy outweigh the risks. Dr. Notelovitz outlines three regimens to achieve compliance in postmenopausal women who wish to avoid menstruation and endometrial sampling. First, a number of studies have shown that continuous administration of estrogen and progestin can reduce withdrawal bleeding and still be acceptable to the patient. Second, the need for endometrial

sampling can be reduced by documenting the bleeding pattern of women on cyclical therapy. Studies have indicated that endometrial hyperplasia will not occur if withdrawal bleeding occurs at 12 days or more after the progestin treatment. And thirdly, the endometrial sampling procedure could be made more acceptable psychologically if it was referred to as a "sampling," rather than a "biopsy" of endometrial tissue. In addition, new techniques now minimize the pain and discomfort associated with this procedure. Dr. Notelovitz presented two case studies to illustrate the importance of compliance in long-term estrogen therapy.

Bone mass measurements using single or dual photon absorptiometers are essential for identifying and documenting the bone mineral status of the patient. Educating patients on the benefits of hormonal therapy on bone mass content and documenting bone mass changes, along with suggesting changes in lifestyle and exercise regimens, may make a positive impact on the health of climacteric women.

Dr. C. Conrad Johnston, Jr., of the Indiana University Medical Center in Indianapolis, discussed approved therapies to restore bone mass, and experimental treatments to prevent further fractures in patients who have already experienced an osteoporotic fracture. He discussed the complex factors involved in the production of fractures, some of which cannot be helped by available therapies, and re-emphasized that the best approach to treatment of osteoporosis is prevention.

Low bone mass is only one cause of increased fractures in the elderly. Both intrinsic and extrinsic factors also influence fracture pathogenesis. Intrinsic factors include osteomalacia, architectural abnormalities, and abnormalities of bone remodeling. Extrinsic factors may involve increased frequency and intensity of trauma.

Methods approved for use to sustain bone mass and prevent subsequent fractures are estrogen therapy, calcium, and calcitonin. The data on estrogen replacement therapy have been discussed in detail by other panel members. Dr. Johnston added that a study reported in the American Journal of Obstetrics and Gynecology in 1987 (*4*) showed the value of starting estrogen therapy near menopause, and its continuing effectiveness in women up to 65 or 70 years of age. Calcium is also used in the prevention of bone loss, and some studies suggest that calcium is effective in reducing the number of subsequent fractures, although the mechanisms by which it does this are unclear.

A recent treatment being used for osteoporosis is calcitonin; several studies of its effectiveness and long-term effects were reviewed. The drug has been shown to increase bone mass; however, after 18–24 months of therapy, the effectiveness of calcitonin is questionable. As discussed earlier, new routes of administration of this drug may make it more promising in the future.

A number of investigational agents being studied for treating osteoporotic patients were described. These include sodium fluoride, low-dose parathyroid hormone, anabolic steroids, cyclic therapy, and growth hormones.

Within this group, more studies have been performed on sodium fluoride. These studies have shown that sodium fluoride can increase spinal trabecular bone by 30–40 percent, yet it does not increase cortical bone mass. Also, the drug is not effective in 10–30 percent of patients, and can produce toxic side effects.

Both low-dose parathyroid hormone and anabolic steroids may increase bone mass. However, a major drawback is the latter's deleterious effect on serum lipids. Growth hormones may also be promising, but more studies will be required to evaluate the ability of these substances to prevent fractures.

The regimen known as Activate, Depress, Free, Repeat (ADFR), or cyclic therapy, may be beneficial to osteoporosis patients. The therapy is based on agents that manipulate the bone remodeling process.

In conclusion, while preventing osteoporosis is key, effective treatments are needed for patients who have already suffered fractures. Further studies on promising investigational therapies may provide improved methods of reducing the incidence of fractures in osteoporotic patients. New, effective methods for increasing bone mass are needed.

References

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