



Diphosphonates in the treatment of osteoporosis

A GREAT DEAL of publicity has been given to a recent study in the *New England Journal of Medicine* concerning the use of etidronate disodium in the treatment of osteoporosis.¹ This landmark study evaluated more than 400 women with postmenopausal osteoporosis at seven major medical centers throughout the mainland United States and Hawaii. The results corroborate an earlier study from Europe that demonstrated a similar effect in a smaller group of patients.² Though the basic designs of the studies were dissimilar, the results were quite similar—an astonishing fact considering the great geographic diversity of the study subjects.

Many studies have been conducted over the years to evaluate the effects of diphosphonates on skeletal metabolism. These drugs are usually employed to treat Paget's disease of bone.³ The diphosphonates are synthetic drugs analogous to pyrophosphate, normally found in the body.⁴ Diphosphonates contain a carbon atom substituted for the oxygen linkage in pyrophosphate. This difference renders the molecule nonhydrolyzable by endogenous pyrophosphatase activity. Various side groups are attached to the phosphate moieties, giving the compounds their individual characteristics.

MODE OF ACTION UNCLEAR

Etidronate disodium is the hydroxyethane derivative of this basic structure. Studies show that the compound can inhibit osteoclastic resorption of mineralized matrix, interfere with the activation and procurement of precursors to osteoclasts, and impair excretion of lysosomal enzymes that cause demineralization of bone.⁴⁻⁶ Osteomalacia has been associated with the drug in various dosages and durations of usage.^{7,8} This observation concerned many investigators, since it posed a potential problem for the drug's use in treating osteoporosis. As

the recent experimental results proved, however, this concern was unfounded.

In the European study, etidronate disodium was administered for 2 weeks every 3 months. After the first year of treatment, an increase in bone density of 5.3% was noted in the lumbar spine, and a decrease in fracture rate of 89% was found in the vertebral skeleton.² The study conducted in the United States was more broad-based.¹ It attempted to determine if an activator of the skeleton, namely phosphorus, was needed before giving the etidronate. The results showed similar increases in bone density and decreases in fracture rates regardless of whether patients had used a skeletal activator. Hence, etidronate itself was the major effector of the phenomenon.

The precise mechanism for the effect of etidronate on the osteoporotic skeleton is unclear. The remodeling process of the skeleton is a composite of biochemically coupled resorption and formation functions. If resorption is slowed by etidronate, the formation aspect may become dominant and deposit a quantum of bone on the existing skeletal matrix. Repeated applications of the drug may add more and more "packets" of bone, leading to the increases in density noted. The mathematical relationship between bone density and fracture rate is such that small increases in density can profoundly influence the fracture rate.

IMPLICATIONS FOR THE FUTURE

Many questions yet remain about the future of this treatment, since reported studies are of limited duration. It is hoped that continued use of the agent produces a linear increase in density rather than a temporary increase followed by a plateau. Calcitonin, approved for the treatment of osteoporosis, increases skeletal density over 12 months and then produces no further increase.⁹

In contrast, sodium fluoride, an agent that has yet to be approved for treatment of osteoporosis, induces a linear increase in bone formation and skeletal density that is noted even up to 4 years.¹⁰ It is hoped that etidronate can produce a linear increase in density over time without the toxic effects that fluoride may produce.

Although etidronate has been used to treat established osteoporosis, it may have greater application in the prevention of early menopausal bone loss and development of osteoporosis. With the high rates of bone turnover in early menopause following the loss of estrogenic activity, osteoclastic activity is increased. An agent that suppresses this enhanced osteoclastic activity, such as etidronate, calcitonin, or estrogen, will prevent skeletal deterioration.

Long-term use of etidronate or any diphosphonate must be evaluated carefully. The complications of long-term estrogen therapy are well known. Extended use of calcitonin may incur an element of tachyphylaxis and loss of efficacy. Long-term use of diphosphonates could bring unexpected complications, although this may be

quite unlikely with low doses. Among the patients who underwent skeletal biopsies in the recent trials, there was no evidence of toxicity.

The regimen for etidronate therapy is simple. The patient takes 400 mg/d etidronate disodium for 14 days every 3 months. Because of low absorption, the drug must be taken on an empty stomach and no food should be consumed for several hours thereafter. Pre- and post-treatment bone density measurements are used to assess efficacy. The drug is not yet approved by the Food and Drug Administration for treatment of osteoporosis. As noted, long-term toxicity is unknown but short-term skeletal toxicity is not a problem. With minimal gastrointestinal side effects, the drug is highly acceptable to patients.

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Erratum

There were errors in the article, "Quality assessment in the medical intensive care unit: evolution of a data model," by Edward D. Sivak, MD, and Alejandro Perez-Trepichio, published in the May 1990 issue, Volume 57, Number 3. In Table 2, page 276, the median age of patients on the gastroenterology service was 60.8 years.

The age range of survivors on the thoracic cardiovascular surgery service was 15 to 79 years, and the age range of nonsurvivors was 52 to 69 years. The median number of pre-ICU days for nonsurvivors on the thoracic cardiovascular surgery service was 66.