

Editorial: Long-Term Safety of Bisphosphonates

Bisphosphonates are widely used to treat osteoporosis. They reduce the incidence of new fractures in patients with established osteoporosis (1, 2). In women with osteopenia, bisphosphonates prevent bone loss, and physicians prescribe them with the hope of preventing future fractures. These medications have profound effects on bone physiology, but the long-term consequences remain unknown. The longest duration of placebo-controlled trials is 6 yr; subjects in observational studies have used the newer amino-bisphosphonates for 10 yr. Some unadvertised aspects of bisphosphonates, including their long half-life and their effects on bone physiology, are not well recognized.

Unlike most medications, bisphosphonates remain in the body for decades. These drugs are not metabolized, but are either excreted renally or deposited within the bones. The amount of drug within the bone will accumulate with use. There is no known method of removing the medication from the bones. The duration of physiological effect is still unknown. After taking alendronate for 5 yr, the bone resorption and formation markers remain suppressed for at least 5 yr after discontinuation (3).

The amino-bisphosphonates strongly inhibit osteoclastic bone resorption. During normal bone remodeling, osteoblastic bone formation follows resorption and occurs within the eroded cavities, so inhibition of bone resorption also results in inhibition of bone formation. Bone biopsy studies using double tetracycline labels show that the bone-forming surface is suppressed by 60–90% with usual doses of the bisphosphonates (4, 5). These drugs are certainly not anabolic! The volume of bone does not increase. The bone density as measured by dual-energy x-ray absorptiometry, however, does increase. This is because the bone is no longer remodeling, and so there is not much new bone. The older bone is denser than the newer bone; there is less water and more mineral in the bone, and the radiographic techniques thus measure the higher density. Osteoporotic bone is generally undermineralized, so some increase in mineralization (or hardening of the bone) may improve the bone strength (6).

Bone that has been treated with bisphosphonate is still able to show an anabolic response to intermittent PTH, although the effect is blunted (7). Thus, fortunately, the profound bisphosphonate suppression of bone formation is at least partly reversible.

By inhibiting bone resorption, bisphosphonates reduce the chance that trabecular plates will perforate. This has been shown with three-dimensional computed tomography scans of bone biopsies. Placebo-treated bones lose bone mass because they continue to have excess bone resorption, which leads to perforation of trabecular plates. This starts a vicious

cycle of additional bone resorption because isolated trabecular rods have lost their mechanical signaling. As bone structure is lost, abnormal stress is placed on the remaining structures, which increases the possibility of damage and further stimulates bone turnover. Osteoblastic bone formation increases, but not enough to replace all of the lost bone or restore the trabecular architecture, so the overall bone mass decreases. The antiresorptive drugs halt this vicious cycle, and we think this is the major mechanism for improving bone strength.

Once bone resorption has been inhibited to a certain degree, there is probably no benefit to further inhibition. Thus, the relative reduction in risk of fractures with antiresorbing medications is not closely linked to the increase in the bone density (8, 9). For example, in the risedronate hip fracture study (1), the decrease in hip fractures with 2.5 mg/d was statistically significantly different from placebo. With 5.0 mg/d, however, the relative risk of hip fractures was not statistically different from placebo, despite a greater bone density. Although combinations of antiresorptive medications may result in greater increases in bone density, the clinical trials have not had enough subjects to show any evidence that fracture risk is further reduced.

A major question is: can potent inhibition of bone turnover be harmful? Two separate but related consequences of this inhibition are increased mineralization and accumulation of microdamage. As bone mineralization increases, the bone becomes brittle. This has been demonstrated by biomechanical measurements of bones that show a wide range of mineralization (10). The brittle bone might be more susceptible to fracture, but we don't know the optimal mineralization density for the human skeleton. Microcracks occur in normal bone after the kind of stresses encountered in day-to-day life. These cracks are detected by the osteocytes, which initiate a bone-remodeling unit to repair the damage. If bone resorption is strongly inhibited, the damage can't be repaired because the osteoclasts won't dissolve the bone. In animals given high doses of bisphosphonates, microdamage accumulation is observed (11). The biological purpose of bone remodeling is probably to remove microdamage and replace it with new bone. If this process stops, the damage accumulates and could eventually weaken the bone.

Thus, our current knowledge of bone physiology suggests that bisphosphonates would increase bone strength by preventing trabecular plate perforation and improving bone mineralization in undermineralized bone. After prolonged severe suppression of bone formation, however, negative effects could occur. Bone could become too brittle and/or accumulate microdamage. We don't know if or when these conditions occur in humans, but it is important to pay attention to reports that could provide clues to long-term effects.

The longest-term results so far are from follow-up studies of women in the first large clinical trials. After a 3-yr ran-

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domized trial of alendronate, 164 women continued to take the medication for a total of 10 yr. An observational uncontrolled follow-up showed that their fracture rate was similar during yr 6–10 to the rate in the original alendronate groups ($n = 597$) during yr 1–3 (12). Data from the follow-up of the Fracture Intervention Trial (FIT) study were recently published (3). Women who had taken alendronate for about 4.5 yr were then randomly given alendronate or placebo for 5 yr. During the last 5 yr, the bone density increased slightly at the spine and was stable at the hip in those taking alendronate but showed some decrease in the placebo group (although not back to baseline). The fracture data, recently presented as an abstract (13), showed no difference in the number of clinical fractures or morphometric vertebral fractures between the two groups during the last 5 yr. These data from clinical trials demonstrate that bisphosphonates are beneficial to the bones during the first 5 yr of use and that continuation for the next 5 yr is no better than discontinuation.

The current paper by Odvina *et al.* (14) reports nine patients who presented with unusual fractures with delayed healing. They had been taking alendronate at the usual doses for 3–8 yr, and bone biopsies showed absence of bone formation by tetracycline labeling. The authors were concerned about the possibility that the alendronate caused an increased susceptibility to, and delayed healing of, the non-spine fractures. It is important to note that these patients did not have osteomalacia, as has been described with etidronate, the first-generation bisphosphonate. Instead, the biopsies resembled the “adynamic bone disease” that has been described in some patients with renal failure. Physicians should not be reassured that newer-generation bisphosphonates are safe just because they don’t cause osteomalacia. Another finding from the paper was that bone biopsies showed more suppression than predicted by the biochemical markers. This has been noted in other bone biopsy studies of bisphosphonates. In the animals, biopsies available from several skeletal locations showed the same severe suppression of bone formation (11), which suggests that the iliac crest is representative of the skeleton in this condition. The reason for the discrepancy between serum markers and bone formation needs additional study, but we must remember that the primary focus is on the bone. The bones could make alkaline phosphatase without making bone, or there could be some basal level of “bone” alkaline phosphatase made by cells other than active osteoblasts.

The study by Odvina *et al.* (14) by itself does not prove that bisphosphonates are harmful to the skeleton. These patients were given bisphosphonates in the first place because their physicians thought they had an increased risk of fractures. The low bone formation rates are expected after treatment with these drugs, and the real cause of fractures could have been the underlying bone disease. The patients were from referral centers, which attract cases with unusual fractures. We have seen patients with similar serious fractures before bisphosphonates were in use. The cases reported here, however, are important because they provide more clues about the potential adverse effects of bisphosphonates.

In summary, many physicians do not even consider the possibility that bisphosphonates could have some adverse effects on the bone. The interesting results described in the

paper by Odvina *et al.* (14), along with reports from animal studies and biopsy data from clinical trials, should heighten awareness of the actions of these drugs. The profound suppression of bone formation could have negative effects that occur after long-term accumulation in the skeleton. There is no good surrogate for the passage of time, and it will be at least a decade before we have any data about whether the potential negative effects would ever predominate over the known positive effects. Until then, bisphosphonates should be used carefully. Men and women with established osteoporosis have a high risk of fragility fractures within the 5 yr after diagnosis, and in these cases the proven benefits outweigh the theoretical long-term risks. These benefits, however, are proven only for the first 5 yr. I believe the current evidence suggests that bisphosphonates should be stopped after 5 yr. Those patients who remain at a high risk of fractures or who have had fractures despite bisphosphonate therapy could be considered for treatment with intermittent PTH. Combinations of anabolic and antiresorptive medications are currently being studied, and the results will be very important. Other schedules and doses of bisphosphonates also should be examined. Perhaps intermittent cycles of drugs will be the choice of the future.

In otherwise healthy perimenopausal women who merely have osteopenia, the best therapeutic option is not clear. Their risk for a fracture within 5 yr of diagnosis is low, but without treatment bone will be lost and lifetime risk of fractures is increased. Observational studies suggest that estrogens continue to prevent fractures after decades of use, and the Women’s Health Initiative found that the profile of adverse effects of initiating estrogen in perimenopausal women was better compared with that in older women (there were fewer strokes, heart attacks, and menopausal symptoms in women on estrogen than on placebo) (15), but there is probably a long-term risk of breast cancer. Selective estrogen receptor modulators exacerbate menopausal symptoms in this age group. Calcitonin appears to be safe and has been in use for decades, but it may not be as effective at fracture prevention. The bisphosphonates in doses used today suppress bone formation to a greater extent than the other antiresorbing medications, so it is possible that microdamage accumulation would develop after 15 or 20 yr—just about the time between menopause and the usual onset of osteoporotic fractures. Certainly this is an issue that requires long-term, carefully designed research.

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