



Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology

EDITORIAL

Bisphosphonates and bone. . .what have we learned?

Although dental educators continually stress to their students the importance of recognizing that the mouth and its contents are merely a part of the entire patient we treat, this important lesson is sometimes overlooked once a diploma is hung on the office wall and the pressures of private practice start to mount. During the past few years the mouth-body interaction has been prominently brought into focus in the dental and medical world, as well as within the lay community by widespread reports of the relationship between periodontal disease and low birth weight premature births, coronary heart disease, cerebrovascular disorders, and kidney maladies to mention a few.

Now come additional medical disorders associated with the use of drugs for which we must reacquaint ourselves. These are diseases that primarily affect long bones and that are commonly treated by the class of drugs known as bisphosphonates (BPNs). These medications suppress the actions of osteoclasts and thereby reduce bone resorption and increase bone density. They have become commonly prescribed to prevent and/or treat osteoporosis (and oftentimes osteopenia, or low bone mass), multiple myeloma, metastases of malignant tumors to bone, and Paget's disease. Since their introduction, they have been widely accepted in the medical community and have for the most part been very useful to accomplish the main goal of preventing fractures and pain in the patients who suffer from the aforementioned diseases.

Of these disorders, osteoporosis is the most common, affecting approximately 10 million Americans. An additional 18 million have osteopenia, which can degenerate into osteoporosis.

The incidence of both is higher in women than in men, with postmenopausal women being more commonly affected. Women older than age 50 account for 20% of the cases. The cause of primary osteoporosis is not fully understood, but is probably attributable to a protracted, mild negative calcium balance, subsequent to a deficient intake of calcium in the diet. Other

etiologies may include an inactive lifestyle, decreased estrogen causing flawed constructive metabolism of protein, and reduced output of the gonads or adrenals. Secondary osteoporosis may be caused by extended treatment with heparin or steroids, malnutrition, malabsorption, alcoholism, and prolonged disuse of the skeleton, as well as numerous endocrine disorders.

A major problem that arises in individuals with osteoporosis is that hip fractures are common following a fall and 20% to 30% of patients who suffer this injury are dead within 1 year. Of those who survive, many require additional assistance in daily living. Furthermore, these patients suffer significant diminution of life quality.

The most common pharmacologic treatment has been through the use of oral bisphosphonates, which have been proposed to help strengthen the skeleton and limit these fractures. Oral bisphosphonates can serve an important function and have become very popular. In fact, nearly 200 million prescriptions have been written worldwide for these drugs.

In the United States, the most commonly used oral bisphosphonates to treat osteoporosis are alendronate sodium (Fosamax), risedronate (Actonel), and relatively recently, ibandronate (Boniva). Stronger forms of bisphosphonates have been given to patients via the intravenous route to treat osseous metastases and primary bone tumors such as multiple myeloma. The most widely used of these are zoledronic acid (Zometa) and pamidronate disodium (Aredia). During the past year, intravenous zoledronic acid has also been introduced as Reclast for once-yearly treatment of osteoporosis.

However, serious side effects have been shown to be induced by both intravenous as well as the oral forms of this class of drugs. During the past 7 years, osteonecrosis of the maxilla and mandible has been reported to the Food and Drug Administration (FDA) in more than 4000 patients taking bisphosphonates. Most of these cases were a consequence of intravenous bisphosphonates.

While not confirmed, the estimated incidence of jaw osteonecrosis induced by oral bisphosphonates is 7 cases per million patient-treatment years. This occurrence following dental extractions with the oral use of these drugs is estimated to be 0.09% to 0.34% and the risk increases when the duration of therapy exceeds 3 years.

It is becoming clearly apparent that the side effects of these nitrogen-containing bisphosphonate drugs increase with the duration of their use by patients as well as their relative potency. This would explain why we did not see the rising incidence of osteonecrosis until these medications had been on the market for several years. Furthermore, we see the most complications from the strongest drug in the group, zoledronate, followed by pamidronate, and then the oral forms, which are about one tenth as powerful as zoledronate.

In addition, it is now becoming apparent that the initially proposed therapeutic effectiveness of alendronate in treating osteoporosis may be significantly less than had been expected. Studies are appearing on a more frequent basis reporting spontaneous femoral fractures in patients who had been taking alendronate for more than 5 years. Physicians are being advised to monitor their patients for low bone turnover rates and offer their patients a drug holiday if they have poor bone regeneration. An excellent test to use for this purpose is the C-terminal cross-linking telopeptide (CTX) evaluation made of a fasting serum sample acquired in the morning. When the CTX returns to an acceptable level, then the drug may be started once again.

So, it is appropriate to query: "Where do we go from here?" On the one hand, we have diseases that require treatment (cancers of the bone or metastatic to it and loss of bone mass). On the other hand there are commonly used medications that seemed to help but are now shown to cause infrequently encountered, but seriously morbid, side effects.

In regard to the use of intravenous bisphosphonates to treat osteolysis associated with malignancy, we can do our best to work cooperatively with the oncologist and the patient in an effort to limit the likelihood of osteonecrosis developing. With the exception of multiple myeloma, in which thalidomide is becoming an increasingly popular alternative, bisphosphonates are currently the favored drugs for treatment. They are efficacious and even though known to induce osteonecrosis of the jaws, it is unlikely that their use will be stopped in the foreseeable future. Since the extraction of a tooth increases the risk of developing this morbidity 7-fold, our goal should be to help avoid this surgical procedure. Oncologists should be made aware that the patient's dental health should be optimized before be-

ginning the intravenous administration of Zometa and Aredia. In fact, the FDA and Zometa manufacturer, Novartis, do recommend that dental examination and appropriate preventive dental care be carried out before to initiation of the bisphosphonate.

Perhaps we should be even more proactive with our medical colleagues and suggest that all dental infection be eliminated and the need for invasive dental procedures be eliminated for the near and intermediate future. In addition, the bisphosphonate infusion should be delayed for at least 1 month until all invasive dental procedures have healed. And finally, patients should be seen by their dentist for evaluation every 4 months once therapy is initiated. Preventive dental treatment works to decrease the incidence of jaw osteonecrosis and should be stressed to our medical colleagues.

When it comes to the prevention and treatment of osteoporosis, I believe that there are alternatives that can be advocated. And one of those options may even include the elimination of bisphosphonate use.

The objective of treating osteoporosis is to stop bone loss and increase the strength and mass of bone to thwart fractures. Unfortunately, there are no available osteoporosis therapies that completely fill that role. As with most diseases, preventing the disease from arising is the best treatment available.

There are ways to take this approach without using bisphosphonates. Patients can change their lifestyles to eliminate osteoporosis cofactors such as cigarette smoking and alcohol intake. They can combat a sedentary existence by exercising regularly. They can improve their diets and ingest adequate amounts of vitamin D and calcium. Physicians can prescribe nonbisphosphonate bone-strengthening drugs such as raloxifene (Evista) and calcitonin (Calcimar) and bone-forming medications like teriparatide (Forteo).

One of the most common inquiries that I get from both my medical and dental colleagues regarding bisphosphonate-induced osteonecrosis of the jaws (BIONJ) is: "How do we deal with the patients who present to our offices needing dental treatment?" While I would remind the reader that this is an editorial and that the following suggestions are not a dictum derived from prospective, randomized, controlled studies, the comments being offered are based on a rigorous ongoing review of the scientific literature and are fortified with the experience of treating thousands of patients taking bisphosphonates and about 35 patients suffering from BIONJ. The treatment protocol for each patient must be carefully individualized and coordinated with the treating physician.

As stated previously, regarding intravenous bisphosphonate use, patients should be seen for definitive dental care before beginning drug therapy, and they should

be followed on a regular basis thereafter. It is the dentist's responsibility to treat those patients in as timely a manner as possible so as to not delay the much-needed anti-osteolytic medications.

Regardless of whether a patient is taking bisphosphonate orally or intravenously, as long as the dental therapy is not invasive, there ought not to be any alteration in the dental or medical treatment protocols. As the dentist would do in any case, care should be taken in procedures ancillary to the focused one. For example, if a rubber dam is being placed before placing a restoration, the clamp should not abrade the soft tissues.

If the patient has been taking an oral bisphosphonate for fewer than 3 years, it is usually not necessary to alter or delay planned oral, bone-exposing, surgery. However, it is prudent to inform the patient of the possibility of bisphosphonate-induced osteonecrosis of the jaws and of potential dental implant failure if that is the proposed treatment. In fact, all patients treated in my office receive an information sheet detailing the potential risks of having oral procedures performed while they are receiving this class of drug.

However, if given the same scenario as above (fewer than 3 years of oral bisphosphonates) and the patient has a significant cofactor such as corticosteroid ingestion or type I diabetes mellitus, one should seriously consider terminating the bisphosphonate for at least 3 months and restarting it following complete healing of the bone and overlying soft tissues. If the surgery is more urgent and cannot be delayed, then the recommendation is to perform the procedure and stop the drug until complete healing is attained.

In the situation where the patient has been on bisphosphonates for more than 3 years, despite the presence or absence of any comorbidities, then, if conditions permit, terminate the drug for 3 months and resume once osseous restoration has been satisfactorily completed.

In addition, for elective procedures on all oral bisphosphonate patients, except those with fewer than 3 years' drug experience, it is useful to perform the serum CTX test as previously noted. The lower the CTX result, the higher the chance for jaw death. Patients with values lower than 100 pg/mL are considered to be at high risk for developing jaw osteonecrosis due to lower levels of bone resorption and remodeling and those with concentrations above 300 pg/mL have virtually no danger.

In any case, the surgery should be as atraumatic as possible. One may even consider an old-fashioned, but newly redescribed, technique of placing a rubber band around the tooth's circumference and allowing the root

to separate slowly from its attachment as the elastic migrates apically.

Although this author is not a major proponent of perioperative antibiotics for most oral surgical procedures, I do prescribe them for these patients in an attempt to help prevent infection in bone that cannot deal well with microbial invasion. Oral doses of penicillin, ciprofloxacin, or erythromycin in conjunction with metronidazole and rinsing with chlorhexidine are used.

Without question, prevention of bisphosphonate-induced osteonecrosis of the jaws is the best approach. However, the malady does occur, albeit far more frequently with parenteral rather than oral drugs, and we must be prepared for treatment of those patients. The thrust of most therapeutic protocols has been conservatism: antibiotics, antimicrobial mouthwash, and stopping the BPN for a specific time period. This latter strategy has been dubbed "taking a drug holiday" and is used to help stabilize an osteonecrotic site, reduce the risk of developing new sites, and reduce clinical symptoms. We have found that after 6 to 12 months there is sometimes spontaneous sequestration of dead bone or resolution of the situation if the area is physically debrided. These salutary effects are noted even though the half-life of BPNs is known to be in excess of 10.9 years.

When the dental and medical communities were first alerted about BIONJ 6 years ago, disastrous results were common when surgical intervention was attempted. The disease was treated in the same general manner as previously encountered osteomyelitic disorders until it became apparent that the extent of the osseous death was so great and that the bone was not responsive to those interventions.

However, in the past couple of years, some oral and maxillofacial surgeons have been getting better results with more aggressive procedures. In general, I reserve this approach for patients whose pain is intractable and when large dosages of narcotic medications have proven fruitless.

If we can find a way to improve the quality of life for these terminally suffering patients it would be most appreciated. In this regard, I arrange a drug holiday with their treating physician. If they are not already taking antibiotics and rinsing with chlorhexidine, they are begun. Although it has been felt that hyperbaric oxygen (HBO) therapy has not been helpful, perhaps used by itself, as it has been in the treatment of osteoradionecrosis, I have had success in using this modality in conjunction with aggressive debridement. Although it is most usual to perform 20 dives preoperatively and 10 postoperatively, my local HBO institution suggested

altering that protocol by increasing to 30 the number of treatments before surgery.

The patient is a 62-year-old woman who had been treated with Zometa intravenously for multiple myeloma and developed BIONJ in all 4 quadrants. She had necrotic exposed bone and significant discomfort that was not controlled with a fentanyl transdermal patch (Duragesic) and oral time-released oxycodone (Oxy-Contin). Following the previously noted protocol (antibiotics, antimicrobial mouthwash, HBO, and aggressive debridement), the patient is now pain free and her wounds have healed without soft tissue breakdown. Her quality of life has improved dramatically. But, I remind the reader once again and emphasize that this result, while quite satisfactory, must be considered anecdotal, until long-term, controlled, prospective studies can be performed.

So what have we learned about bisphosphonate-induced osteonecrosis of the jaws during the past 6 years? Well, there is some good news: the overall risk of developing the disease appears low, even when patients have concomitant risk factors. At the current time, there is no evidence to support withholding BPN therapy in cancer patients at risk for developing skeletal complications secondary to metastatic bone disease. There is confirmed clinical benefit of using BPNs in these individuals that outweighs the potential morbidity. On the other hand, there may be no advantage to taking oral bisphosphonates for longer than 5 years.

However, the negative outcomes can be severe and our efforts need to be directed at prevention and early detection of BIONJ to help prevent loss of the maxilla and mandible. Dental practitioners would be wise to inquire about bisphosphonate usage on the medical history questionnaires of those they are treating. When patients are, or have recently been, taking BPNs, dentists should try to avoid extractions and other invasive procedures. And, for their part, our medical colleagues need to encourage patients to see their dentists before initiating intravenous BPNs and on a regular basis thereafter.

Perhaps the future will bring us new drugs or techniques to treat the bone-wasting diseases mentioned on these pages that will spare patients the morbidity associated with those currently available. Until that time comes, the dental and medical communities must join in helping to prevent and to initiate early identification and treatment of this potentially widespread destructive condition whose incidence is rapidly expanding.

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