BISPHOSPHONATES AND BONE

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1. CHEMISTRY AND ACTIVITIES

Bisphosphonates, called diphosphonates in the past, have become widely used for various diseases of bone and calcium metabolism. Knowledge of their characteristics was derived from early studies with pyrophosphate. Pyrophosphate is abundant in biological fluids, including saliva, and was shown to inhibit mineralization, but is hydrolysable. Nevertheless it can be used in scintigraphy and as an anti-tartar agent in toothpaste. Synthetic analogs that were used as antiscaling agents in washing powder, the bisphosphonates, are more stable because of the carbon substitution for oxygen (Figure 1). Like pyrophosphate, they disturb the crystallization of calcium phosphate and inhibit its dissolution in vitro and inhibit calcification in vivo. The P-C-P backbone allows for a large number of compounds with different side chains; they all have a strong affinity for metal ions like calcium and iron and are completely resistant to enzymatic hydrolysis. The second activity of these compounds is that they inhibit osteoclastic bone resorption. The anti-resorptive activity varies greatly from compound to compound, but the effects on mineralization do not. Thus, research has focused on developing bisphosphonates with potent anti-resorptive effects so that they can be used at low enough concentration without significant effects on mineralization. The anti-resorptive potencies of recently developed bisphosphonates, like zoledronate, are 10,000 more than etidronate, the first bisphosphonate. Stereoisomers of a compound can have 10-fold differences in potency. Derivatives with an amino group are highly active, but a primary amine is not necessary for potency.

2. MODES OF ACTION

There are multiple mechanisms of action. Even at low doses, bisphosphonates accumulate in bone by binding to mineral crystals. Radiolabeled studies show that bisphosphonates like alendronate preferentially deposit, not in newly formed bone, but beneath osteoclasts. The hypothesis is that osteoclasts ingest the concentrated drug as they resorb the tainted matrix; thereupon, they lose the ruffled border that is the site of resorption, retract from the bone, and undergo apoptosis. Recent studies show that the potent nitrogen-containing bisphosphonates act as analogues of isoprenoid diphosphate lipids involved in the mevalonate biosynthesis branch pathway. They inhibit the biosynthesis of isoprenoid lipids that are essential for post-translation al farnesylation and geranylgeranylation of small GTPase signaling proteins that prevent apoptosis (1). Other mechanisms involving indirect effects mediated through osteoblasts are also likely. Other actions include stimulation of a non-selective cation channel that is abrogated by a tyrosine phosphatase inhibitor, and extraskeletal activities on, for example, angiogenesis and peripheral T cells. Far less is known about mechanisms of the non-nitrogen-containing bisphosphonates.

3. PHARMACOKINETICS

Bisphosphonates are poorly absorbed, with various oral forms having 1 to 10% bioavailability. Absorption occurs in the small intestine and is inhibited when taken with meals, calcium, coffee, or orange juice. The package insert states that bioavailability “decreased (by approximately 40%) when 10 mg alendronate was administered either 0.5 or 1 hour before
The circulating half-life of bisphosphonates is short, between 0.5 and 2 hours, with rapid uptake into the bone during the first passage. Between 30 and 70% of the absorbed bisphosphonate accumulates in the bone, with the remainder excreted in the urine.

Because bisphosphonates accumulate in bone matrix and their removal depends upon turnover of matrix, they may accumulate and persist in the matrix for many years. Estimates for endurance in human cancellous bone are for more than 10 years. That raises the possibility of developing regimens of intermittent administration with periods of abstinence.

4. CLINICAL UTILITY OF BISPHOSPHONATES

In the 1980’s and 90’s, etidronate, the most potent antimineralization bisphosphonate, had been advocated for prevention of heterotopic ossification following spinal cord injury or total hip arthroplasty, but recent understanding is that it only delays mineralization, which resumes upon discontinuation of treatment.

Bisphosphonates are the therapy of choice for Paget’s disease. All bisphosphonates are effective in decreasing bone turnover as assessed by calcium excretion and biochemical markers of bone resorption and formation.

Intravenous bisphosphonates are used for hypercalcemia of malignancy, multiple myeloma-related osteolysis, and patients with documented bone metastases from solid tumors in conjunction with standard anti-neoplastic therapy. As an example, zoledronic acid is administered monthly at a dose of 4 mg infused over a period of 15 minutes and may be continued indefinitely.

Randomized, placebo-controlled studies show the efficacy of bisphosphonates in the management of osteoporosis. A recent analysis of alendronate trials extended for 10 years showed meaningfully increased bone mineral density (BMD) and decreased vertebral fractures in the initial 3-year treatment study (2). The subset of subjects treated daily for 10 years showed further dose-dependent increases in BMD and persistence of the suppression of bone turnover markers. Although the follow-on study did not use incidence of fracture as an efficacy measure but, curiously, only as a safety measure, the authors conclude that the equivalence in cumulative fractures means that there was no adverse effect of the drug. Of note, many benefits seen during the 3-year study were maintained to some degree in the group that was followed after discontinuation. The very gradual loss of benefit is unlike the abrupt bone loss shown in other studies when estrogen is discontinued. Oral bisphosphonates remain the mainstay therapy for senile and glucocorticoid-induced bone loss in men (3).

Intravenous bisphosphonates (especially pamidronate) have been used off-label for children with severe osteogenesis imperfecta (OI), fibrous dysplasia, juvenile osteoporosis, Gaucher’s disease, and glucocorticoid-induced osteoporosis (4). Uncontrolled studies indicate a reduction in fractures after initiation of treatment. In addition, uncontrolled studies report decreased bone pain and improved mobility in children with OI or juvenile osteoporosis.

Because of the potent anti-resorptive effects of bisphosphonates, they have also been used in other settings such as established periodontal disease in postmenopausal women (5).

Recent studies suggest broader applications for bisphosphonates related to orthopedic matters. Because of the understanding that osteoclasts mediate bone loss in aseptic loosening of prostheses, there have been a number of randomized, case-control trials of the use of bisphosphonates in arthroplasty patients. A recent meta-analysis concluded that, although there is a suggestion that bisphosphonates have a beneficial effect in maintaining periprosthetic BMD especially in knees and in arthroplasties with cement, evidence at this time is not complete nor strong enough to generalize the findings or to extrapolate to more meaningful clinical outcomes such as function and revision rates (6).

Animal studies suggest additional orthopedic uses of bisphosphonates. For example, a study in rats showed that systemic alendronate inhibited local bone resorption around the screws of external fixators (6), but it was not clear whether the 5-week timepoint was appropriate as a model for a permanent implant or for a temporary, then unloaded screw (7). Another rat study on early fixation of screws showed that systemic or local bisphosphonate treatment improved mechanical measures of implant fixation (8). Another study used a rat anterior cruciate ligament transection model of osteoarthritis in which systemic administration of alendronate suppressed subchondral bone resorption and prevented the subsequent increase in bone formation and osteophyte formation (9), but there have been no trials that indicate efficacy in OA patients.

5. SIDE EFFECTS, COMPLICATIONS, AND CONCERNS

It is appreciated that oral bisphosphonates can cause upper gastrointestinal disorders such as dysphagia, esophagitis, and esophageal or gastric ulcer. Patients with extreme kyphosis may have difficulty following the directions for the tablets and some may be able to use the liquid forms. Hypocalcemia and lethargy are associated with overdosage. Central nervous system toxicity has been observed in patients beginning therapy, especially with the higher dose (70 mg), once-weekly tablet. Symptoms include auditory and visual hallucinations and visual disturbances. Individual differences in absorption may contribute to side effects and toxicity.

In 2003, a case study reported the development of osteopetrosis, or marble bone disease, in a child who had received pamidronate for 2 and 3/4 years because of low bone density (10). Eighteen months after his last dose of pamidronate, he had osteosclerosis upon x-ray and histological osteopetrosis, or marble bone disease, in a child who had received pamidronate for 2 and 3/4 years because of low bone density (10). Eighteen months after his last dose of pamidronate, he had osteosclerosis upon x-ray and histological osteopetrosis, i.e. endurance of cartilage bars and absence of osteoclasts on bone surfaces, with negative genetic tests. That case report prompted a review of the merits of bisphosphonate treatment in children (4). Although safety and efficacy have not been established in controlled trials in children, experience with bisphosphonates indicates that short-term treatment benefits children with low BMD. Bisphosphonates decrease bone pain.
and improve mobility in children with OI or osteoporosis, and there seems to be no impairment of healing or linear growth. Dosing, duration of treatment, safety of cumulative doses, and proper monitoring tests are not well established and, thus, it was recommended that their use in children be reserved for clinical trials and for management for lytic lesions limited to 2 to 3 years (4, 11).

Because bisphosphonates inhibit the remodeling of bone matrix, there have been theoretical concerns about risks of hypermineralization (12) and accumulation of microfractures (13) with their continuous administration. A recent report of bone biopsy data from 9 patients with osteoporosis or osteopenia who had received oral alendronate and sustained nonspinal fractures (most in unusual locations) showed absence of double-tetracycline label and markedly suppressed bone formation in both cancellous and cortical bone (14). Six of the subjects had inadequate healing of the fracture while taking alendronate and four, after discontinuation. The histomorphometric patterns resembled adynamic bone or low turnover bone of hemodialysis patients and was termed biopsy-proven severely suppressed bone turnover (SSBT). Other factors may have contributed to their SSBT; some subjects had also received glucocorticoids or estrogen, had comorbidities, and had inconsistent biochemical markers of bone turnover. Nevertheless, orthopedic surgeons should be alert to the possibility that patients with spontaneous non-spinal fractures, especially of the femoral shaft, or with delayed fracture healing may have SSBT. Patients also receiving glucocorticoids or estrogen along with bisphophonates should be monitored carefully, as those groups fractured earlier than those receiving only bisphosphonates.

Alarming reports have recently appeared concerning links between bisphosphate therapy and osteonecrosis of the jaw. An academic oral/maxillofacial surgeon, Dr. S. Ruggiero, was sent 63 patients with devastating necrotic lesions of jaw in a 2 and 1/2 year period and was prompted to review them because of the previous rarity of such cases (15). He found that 56 patients had received IV bisphosphonates in the course of anticancer therapies and 7 had received chronic oral bisphosphonates for osteoporosis. Eighty-six percent of the patients had received minor invasive oral surgery such as tooth extractions; 6 of those showed radiographic evidence of osteolysis prior to extraction. Several sustained jaw fractures and nearly all had exposed bone and secondary infections. Most had ischemic changes in maxillary or mandibular bone with widespread necrosis and osteomyelitis; biopsies showed necrotic bone and no evidence of tumor or metastasis. Most were refractory to conservative debridement and antibiotic therapy. In the majority, the involved bone needed to be removed. The apparent selective involvement of the mandible and the maxilla, the latter being a highly vascularized bone, is unexplained, but the antiangiogenic action of bisphosphonates has been invoked in the pathophysiological mechanism. A term has been suggested for this new clinical entity, “bis-phossy jaw”, to refer back to the 19th century disease, phossy jaw (phosphorus necrosis) that was common with exposure to phosphorus. That similarity suggests special vulnerability of the jawbones. Dentists and oral surgeons are now cognizant of this entity and warn patients, even those receiving oral bisphosphonates, about risk of invasive procedures. Since that publication, there have been other corroborating reports, case reports, and alerts. Experts quoted in a newspaper article have collected another 60 or 70 cases in osteoporotic patients receiving oral bisphosphonate (USA Today March 14, 2005) and cases are being assembled at Harvard. The FDA issued an order that manufacturers send warning letters to healthcare professionals and that all bisphophonate labels should mention osteonecrosis.

The estimate of 20 million patient-years’ experience with alendronate alone raises the possibility of chance associations for these problems. Surveillance and more research are needed to identify risk factors for osteonecrosis and delayed bone healing in patients receiving bisphosphonates. In a study of bone fusion with iliac crest bone graft in the rabbit model, alendronate appeared to inhibit or delay bone fusion (16). There are contradicting animal studies reporting that bisphosphonates enhance, inhibit, and have no effect on bone formation around or ingrowth into implants. There is no clinical literature on outcomes in orthopedic surgery for patients receiving bisphosphonates.

7. SUMMARY

Bisphosphonates are potent drugs that have multiple actions, with many new actions being studied. They are effective in treating osteoporosis in both women and men. Infusions of bisphosphonates are useful in managing bone pain and osteolysis in cancer patients. Infusions of bisphosphonates are being used off-label for severe pediatric diseases such as OI and juvenile osteoporosis, but there is insufficient information about their long-term safety. Recent alarming reports of serious complications such as osteoporosis, unusual fractures, delayed healing of fractures, and jaw osteonecrosis emphasize the need for vigilance in surveillance and more research before extending use of bisphosphonates for other applications. From recent reports, it appears that discontinuing bisphosphonates does not reduce the course of osteonecrosis of the jaw or incidence of or delayed healing of unusual fractures. Nevertheless, those reports do not diminish the important role of bisphosphonates in managing bone loss.
References


