Bisphosphonates

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Bone resorption and formation are normally linked and therefore maintain bone strength. When the metabolic linkage is altered, bone structural and material properties decline. Postmenopausal and glucocorticoid-induced osteoporosis, Paget's disease of bone, and fibrous dysplasia are some of the conditions in which there is high-turnover bone resorption, leading to bone with impaired structure susceptible to fracture. Low bone mineral density (BMD) occurs when the rate of resorption exceeds that of formation. High-turnover states ensue with disproportionately increased osteoclastic activity, resulting in increased resorption. Bisphosphonates interfere with osteoclast activity and thus decrease the rate of bone resorption. Similarly, metastatic disease of bone, especially the lytic phase, appears to be mediated by both osteoclastic resorption and other mechanisms. The use of bisphosphonates has dramatically changed the clinical course of some patients with cancer by decreasing the morbidity of skeletal involvement.

Structure and Mechanism of Action

Bisphosphonates are pyrophosphate analogues in which the oxygen in P–O–P has been replaced by a carbon, resulting in a metabolically stable P–C–P structure resistant to enzymatic destruction. Bisphosphonates have two side chains: R1 affects binding affinity to bone; R2 affects antiresorptive capacity and, possibly, side-effect profile. Bisphosphonates vary in potency based on these specific side chains (Fig. 1). Etidronate is a non–nitrogen-containing bisphosphonate with a simple alkyl side chain, whereas pamidronate and alendronate contain basic aminoalkyl groups. Risedronate and zolendronate contain heteroaromatic rings with nitrogen-containing side chains. Tiludronate is a sulfur-containing bisphosphonate.

First-generation bisphosphonates, such as etidronate and clodronate, inhibit bone formation and bone resorption equally. With each successive generation, there has been increased potency, with more selectivity for inhibition of resorption and less inhibition of bone formation. Second-generation bisphosphonates include pamidronate and alendronate; the third generation includes the highly potent risedronate and zolendronate.

Bisphosphonates have a particular affinity for areas of increased bone turnover, such as in metastatic bony lesions and Paget's disease. They primarily work by inhibiting osteoclast function using two main mechanisms. First, bisphosphonates have a high affinity for hydroxyapatite of bone, binding to it irreversibly and therefore inhibiting osteoclast-resorbing surface. Second, absorbed bisphosphonates inhibit osteoclast function by interfering with their critical biologic pathways. Short-chain bisphosphonates such as clodronate inhibit the Krebs cycle; long-chain bisphosphonates such as alendronate inhibit the fatty chain pathway and the ability to form biologic membranes. Bisphosphonates also exhibit apoptotic effects on osteoclasts.

Pharmacokinetics

Oral bisphosphonates have a very low bioavailability and poor gastrointestinal absorption rates (from <0.7% for alendronate and risedronate to 6% for etidronate and tiludronate). Oral absorption can be diminished even further in the presence of mineral water, other liquids, or food in the stomach. Absorbed bisphosphonate remains mainly in the skeleton for prolonged periods (half-lives of 1.5 to 10 years), whereas nonincorporated bisphosphonate is excreted in the urine within two passes through the kidney.

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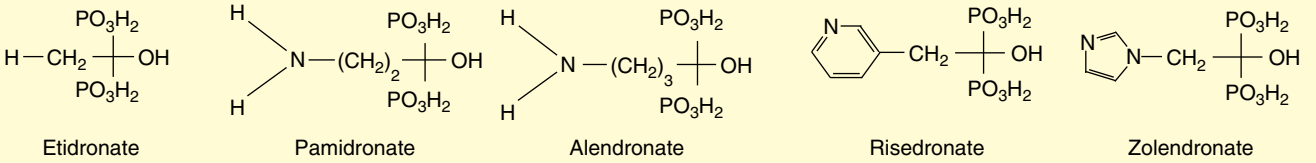

Figure 1 Structural formulas of five bisphosphonates.

Indications for Use

Indications for bisphosphonates include such conditions as postmenopausal and glucocorticoid-induced osteoporosis, Paget's disease, osteolytic and osteoblastic bone metastases, and other orthopaedic problems, such as fibrous dysplasia, heterotopic ossification, and myositis ossificans. Off-label uses are supported by results of controlled clinical trials.

Many bisphosphonates have been shown to be efficacious in the management of postmenopausal and glucocorticoid-induced osteoporosis. Currently, however, only oral alendronate and risedronate are approved for both the prevention and treatment of osteoporosis. Oral bisphosphonates reduce the risk of hip fracture by as much as 50%. Because of the incidence of gastrointestinal symptoms with oral bisphosphonates, treatment with intravenous pamidronate and zolendronate may be indicated for patients unable to tolerate even weekly dosages of oral alendronate and risedronate.

Alendronate has been proved to be effective in postmenopausal osteoporosis. In 2,027 women with preexisting vertebral fractures, alendronate 5 mg daily for 24 months, then increased to 10 mg, resulted in fewer radiographic vertebral fractures in the treatment group.[1] Risk of clinical fracture was 13.6% in the alendronate group versus 18.2% in the placebo group. There was an average increase in lumbar spine BMD of about 5% after 1 year, then 1.5% per year for the next 2 years. At the end of 3 years, there was an increase in BMD of about 6% in the femoral neck and about 7% in the trochanter. In the Fracture Intervention Trial,[2] 3,658 osteoporotic women with either vertebral fracture or osteoporosis at the femoral neck were treated with alendronate for 3 to 4 years. There was decreased risk of fracture in the treated women, with relative risks of 0.47 for hip fracture , 0.52 for radiographic vertebral fracture, 0.55 for clinical vertebral fracture, and 0.70 for all clinical fractures. Alendronate has marked efficacy for men and for individuals on steroids. A single weekly dose is as clinically effective as daily dosage but with lower incidences of dyspepsia, esophagitis, and gastroesophageal reflux disease (GERD).

Risedronate also is effective in increasing BMD and reducing fracture risk. An oral daily dose of risedronate (5 mg) resulted in BMD increases after 6 months of therapy, and at 24 months, lumbar spine BMD increased from baseline by 4%, with increases of 1.3% and 2.7% in the femoral neck and femoral trochanter, respectively.[3] In 2,458 postmenopausal women, those receiving oral risedronate 5 mg daily increased BMD by 3% to 4% in the femoral neck, femoral trochanter, and lumbar spine at 3 years.[4] Risk of new vertebral and nonvertebral fractures also decreased. A single weekly oral dose of 35 mg is as effective as a daily dosage. Risedronate diminishes the hip fracture rate by 50%.

Parenteral pamidronate also has been successfully used in the treatment of osteoporotic postmenopausal women intolerant to oral bisphosphonates. In 36 patients, five courses of cyclical intravenous pamidronate was effective in reducing bone turnover.[5] Thirteen patients who received 30 mg of pamidronate intravenously over 3 months had an increased BMD of 6.2% in the lumbar spine and 4.7% in the hip.[6] To date, no fracture rate data have been reported for pamidronate.

Parenteral zolendronate administered at annual intervals produced effects on bone turnover and BMD comparable to those seen with oral bisphosphonates in the treatment of postmenopausal osteoporosis. In one trial, increases in the treatment group were 4.3% to 5.1% higher for the spine than in the placebo group ($P < 0.001$), with suppressed biochemical markers of bone formation.[7] No fracture prevention data for zolendronate are currently available.

Etidronate, alendronate, risedronate, and tiludronate are all efficacious in the management of Paget's disease. A 400-mg daily dose of etidronate for 6 months, a 40-mg daily course of oral alendronate for 6 months, a 30-mg daily dose of risedronate for 2 months, or a 400-mg daily dose of tiludronate for 3 months controls Paget's disease.[8] In addition, several intravenous infusions of pamidronate are effective.

Bisphosphonates can affect patients with bony metastatic disease in a number of ways. They control hypercalcemia, reduce bone pain, delay skeletally related events (SREs), reduce the number of pathologic fractures, and, in some cases, prolong survival. Initially, oral clodronate and, subsequently, intravenous pamidronate

have been shown to reduce the number of vertebral fractures in patients with myeloma.[9] In a pooled group of 1,962 women with advanced breast cancer, administration of pamidronate 90 mg reduced the rate of SREs by a mean of 30%.[10] All studies showed a delay in the median time to SREs. Zolendronate has been shown to be as effective as pamidronate and should be combined with either chemotherapy or hormonal therapy in women with metastatic bone disease. Zolendronate 4 mg in a 15-minute infusion has been utilized in hormone refractory prostate cancer metastatic to bone. Results showed a statistically significant advantage over placebo in delaying the first SRE ($P = 0.011$), a reduced proportion of patients having SREs ($P = 0.021$), and decreased overall skeletal morbidity ($P = 0.006$).[11] Zolendronate is the first bisphosphonate shown to be effective in both lytic and blastic metastatic disease.

Pamidronate decreases fractures in osteogenesis imperfecta, controls Paget's disease, and reverses the bone changes of fibrous dysplasia. Alendronate has been used off-label for fibrous dysplasia.[12] Furthermore, oral and intravenous etidronate may be helpful in treating fibrous dysplasia. Bisphosphonates work by inhibiting the bone mineralization of ectopic bone matrix that can occur in acute episodes.

Drug Interactions and Adverse Effects

Bisphosphonates generally should not be taken with antacids that contain aluminum or magnesium, bottled water containing minerals, or calcium supplements because these agents decrease bisphosphonate absorption. In addition, food renders bisphosphonates ineffective; a 2-hour interval between meals and the administration of a dose is recommended. Aminoglycosides taken with bisphosphonates may cause severe hypocalcemia.

Adverse effects from oral bisphosphonates include gastrointestinal complications such as gastritis or esophagitis, abdominal pain, nausea, vomiting, diarrhea, and constipation. To minimize gastrointestinal inflammation and ulcer, patients should remain upright (sitting or standing) for at least 30 minutes after taking the medication. In patients with a questionable history of GERD, incremental dosage increases are advisable. For example, one dose (alendronate 70 mg) can be given the first month, then every 2 weeks, then weekly while monitoring for evidence of intolerance. Tolerance is generally improved with once-weekly rather than daily dosing. Electrolyte disturbances such as hypocalcemia and hypophosphatemia may occur. Renal impairment may result, and bisphosphonates should be used sparingly in patients with renal insufficiency. Etidronate impairs mineralization of newly formed bone and may result in osteomalacia and fracture if taken in large doses. Less common reported side effects include hallucinations, taste disorders, pseudomembranous colitis, iritis, arthralgia, pericarditis, hepatotoxicity, and scleritis. Overdosage of bisphosphonates may result in hypocalcemia.

Intravenous pamidronate and zolendronate may cause bone pain, fever, and malaise. Bone pain may be more likely to occur when intravenous infusions of these bisphosphonates are taken without calcium. Influenza-like symptoms may be particularly associated with intravenous bisphosphonates but may be managed with diphenhydramine and acetaminophen before infusion. Furthermore, adverse side effects may be minimized with increased infusion time and volume.

Bisphosphonates are contraindicated in patients with hypocalcemia or severe renal impairment (creatinine clearance <30 mL/min) and in those who cannot remain upright for at least 30 minutes. In addition, bisphosphonates should generally be avoided in those with symptomatic GERD, gastrointestinal bleeding, Crohn's disease, or malabsorption syndromes; in women of childbearing age; and in patients who have been receiving bisphosphonate therapy for 7 years. Studies have shown that alendronate used for 7 years in postmenopausal osteoporosis was well tolerated and effective. While no studies link bisphosphonates to birth defects in humans, animal studies have linked bisphosphonates with fetal abnormalities. The effect of bisphosphonates in delaying fracture healing has been raised.[13] Peter et al[14] showed no delay in fracture repair and mechanical restoration but did show retardation of callus remodeling.

Dosage and Cost

Bisphosphonates are available for both oral and intravenous administration. Dosages and costs are dependent on the condition being treated and length of therapy (Table 1).

Summary

Bisphosphonates are powerful antiresorptive agents appropriate for use in patients with many metabolic bone disease states. They are effective in enhancing bone density in patients with structurally flawed bone and in minimizing morbidity and mortality by preventing fractures. Furthermore, they appear to be cost efficient and safe for short-term use in humans. While oral bisphosphonates may increase the risk for gastrointestinal complications such as esophagitis, adhering to the

Table 1
Dosages of Bisphosphonates and Costs* in Selected Conditions

Condition	Etidronate	Alendronate	Risedronate	Pamidronate	Zolendronate	Tiludronate
Osteoporosis treatment† (cost/yr)	400 mg/d × 14 d q 3 mo ($432.88)‡	10 mg/d or 70 mg/wk ($919.08§)	5 mg/d or 35 mg/wk ($871.08§)	30 mg q 3 mo ($1,155.00)‡	4 mg/yr ($988.99)‡	N/A
Osteoporosis prevention	N/A	—	35 mg/wk	N/A	N/A	N/A
Paget's disease (treatment course)	400 mg/d × 6 mo ($1,391.88)	40 mg/d × 6 mo ($1,181.94)	30 mg/d × 2 mo ($1,047.98)	90 mg ($866.25), then 30 mg q 3 mo ($288.75)	N/A	400 mg/d × 3 mo ($1,185.97)
Bone metastases	N/A	N/A	—	90 mg q 4 wk	4 mg q 3-4 wk	N/A
Hypercalcemia of malignancy	7.5 mg/kg/d × 3 d	15 mg	N/A	90 mg PRN	Single 4-mg doses PRN	N/A
Fibrous dysplasia	N/A	70 mg/wk‡‖	N/A	60-90 mg q 2 mo‖	N/A	N/A

* Costs at a large chain discount suburban pharmacy in Stamford, CT, December 2002. Does not include dispensing fee.
† For postmenopausal women, men, and glucocorticoid-induced.
‡ Off-label use in the United States
§ Once-weekly dose
‖ Until N-telopeptide plateaus
N/A = not applicable

specific instructions as well as switching to a once-weekly dose may minimize the risk. Intravenous bisphosphonates are appropriate in patients with Paget's disease and metastatic osteolytic bone metastases and are being used off-label in osteoporotic patients unable to tolerate oral bisphosphonates. Bisphosphonates are the agent of choice for the treatment of osteoporosis and Paget's disease.

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