Safety of Bisphosphonates

Catalina Orozco, MD[a], Naim M. Maalouf, MD[b,*]

KEYWORDS

• Bisphosphonate • Safety • Side effects • Osteonecrosis of the jaw
• Atypical femoral fracture • Atrial fibrillation • Esophageal cancer • Esophagitis

KEY POINTS

- Although placebo-controlled clinical trials lasting 3 to 4 years have shown that bisphosphonates significantly reduce the risk of osteoporotic fractures, limited data are available on their antifracture efficacy beyond 5 years of therapy.
- Common side effects of bisphosphonates include upper gastrointestinal tract irritation with oral bisphosphonates and an acute phase response with intravenous bisphosphonates.
- Osteonecrosis of the jaw and atypical femoral fractures have emerged as rare complications associated with long-term bisphosphonate use, and the incidence of these complications may increase with duration of bisphosphonate exposure.
- The association of bisphosphonate therapy with esophageal cancer and atrial fibrillation is not well substantiated.
- Necessity of continued bisphosphonate therapy should be periodically reassessed after 5 years of therapy in patients with osteoporosis.

INTRODUCTION

Bisphosphonates are antiresorptive medications that reduce osteoclastic activity, resulting in decreased bone turnover, improved bone mineral density, and reduced risk of osteoporotic fractures. As of 2008, bisphosphonates were used by more than 5.1 million patients in the United States alone, with a prevalence of approximately 12% among women older than 55 years.[1] Although overall well-tolerated in large-scale osteoporosis clinical trials, several adverse events have been reported with their use in clinical trials and in the postmarketing era. This article discusses the safety of bisphosphonates for the treatment of osteoporosis, identifies at-risk populations for these side effects, and provides guidance for their use.

[a] Rheumatology Associates, 8144 Walnut Hill Lane, Suite 800, Dallas, TX 75231, USA;
[b] Department of Internal Medicine, Center for Mineral Metabolism and Clinical Research, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390-8885, USA
* Corresponding author.
E-mail address: naim.maalouf@utsouthwestern.edu

Rheum Dis Clin N Am 38 (2012) 681–705
http://dx.doi.org/10.1016/j.rdc.2012.09.001 **rheumatic.theclinics.com**
0889-857X/12/$ – see front matter

PHARMACOLOGY OF BISPHOSPHONATES

Mechanism of Action

Bisphosphonates consist of a group of compounds with a common phosphorus-carbon-phosphorus backbone that resembles the phosphorus-oxygen-phosphorus structure of native pyrophosphate,[2] and different side chains that are specific to each compound. Their major pharmacologic property is inhibition of bone resorption, which is achieved through (1) strong attachment to the hydroxyapatite mineral found in bone, (2) uptake by osteoclasts resorbing bone, and (3) inhibition of osteoclast function or induction of osteoclast apoptosis.[2,3] Reduced bone resorption results in improvement in bone mineral density and reduction in fracture rates. Bisphosphonates secondarily reduce bone formation due to the normal "coupling" between bone resorption and bone formation that occurs at individual resorption units.

Pharmacokinetics

Because of their high affinity to hydroxyapatite, bisphosphonates exhibit unique pharmacokinetic properties: after the ingestion of an oral bisphosphonate, less than 1% of the drug is absorbed from the gastrointestinal tract, whereas intravenous bisphosphonates are injected directly into the circulation. Of the fraction that reaches the circulation, approximately 50% is excreted unmetabolized in the urine, and the remaining 50% is taken up avidly in the skeleton, with little uptake by other tissues. Thereafter, bisphosphonates are slowly released back into circulation after uptake by osteoclasts at the surface of bone, and a much slower elimination phase is seen, with an estimated mean terminal half-life of greater than 10 years.[4]

Pharmacology of Different Bisphosphonates

The mechanism through which osteoclast dysfunction occurs differs between nitrogen-containing bisphosphonates and non–nitrogen-containing bisphosphonates, or simple bisphosphonates. The nitrogen-containing bisphosphonate group (which includes alendronate, ibandronate, risedronate, and zoledronic acid [ZA]) exerts its effects through inhibiting the enzyme farnesyl pyrophosphate synthase (FFP synthase) that prevents the prenylation of small GTPases, thus reducing osteoclast activity. On the other hand, simple bisphosphonates (etidronate, clodronate, and tiludronate) are metabolized in the osteoclast cytosol to ATP analogs that induce osteoclast apoptosis.[5] Even among the widely used nitrogen-containing bisphosphonates, the potency of individual bisphosphonates is further determined by the degree of affinity to hydroxyapatite and the extent of inhibition of FFP synthase.

EFFICACY OF BISPHOSPHONATES

Currently 4 bisphosphonates are approved by the U.S. Food and Drug Administration (FDA) for the treatment of osteoporosis in the United States: alendronate, ibandronate, risedronate, and ZA. All 4 medications have been shown in FDA registration trials[6–9] to reduce the risk for vertebral fractures over a 3-year period. In these trials, some of these medications also significantly reduced hip fractures (alendronate and ZA) and nonvertebral fractures (risedronate and ZA).[6,8,10] In addition to the FDA registration trials, data from nonregistration trials and pooled or observational data have supported a reduced rate of vertebral, nonvertebral, and hip fractures for all 4 agents.[11–14] Overall, point estimates of relative vertebral fracture risk reduction range from 40% to 70%, and relative hip fracture reduction ranges from 40% to 50% with these drugs. This relative reduction risk for fractures seems to only be partly explained by improvement in bone mineral density, as evidenced by the nonlinear relationship between bone density and fracture reduction.[15,16]