PHARMACOLOGY

What do you really need to know about bisphosphonates?

Jason H. Goodchild, DMD ■ Mark Donaldson, BSP, ACPR, PHARMD, FASHP, FACHE

Despite being synthesized in the late 1800s, bisphosphonates have only been used clinically for the last 5 decades. In fact, on the 50th anniversary of the first clinical use of a bisphosphonate (1968, etidronate disodium), it is interesting to remember that the origin of bisphosphonates stems from dental research. In the 1960s, Procter & Gamble was hoping to develop a topical agent for use against dental calculus. By the end of the decade, their researchers were working with analogs of pyrophosphate, the disphosphonates, which had a similar structural backbone to the former but centered around a \(-P–C–P–\) bond instead of a \(-P–O–P–\) bond (Figure). Conformationally, in 3 dimensions this structure created a “bony hook,” resulting in a high affinity of these compounds for hydroxyapatite in bone.

Following successful treatment of a young girl who had myositis ossificans progressiva and subsequent studies, etidronate (Didronel) was granted regulatory approval in 1977 for several indications, including Paget disease and hypercalcemia of malignancy. Today, 7 bisphosphonates are approved for use in the United States. They are indicated for the prevention and treatment of osteoporosis, multiple myeloma, Paget disease of bone, bone metastasis (with or without hypercalcemia), osteogenesis imperfecta, fibrous dysplasia, primary hyperparathyroidism, and other conditions resulting in bone fragility. Clodronate is approved in 67 countries, excluding the United States.

Although bisphosphonate research originally focused on uses to remove dental calculus, the last 50 years has seen this class of drugs grow in medicine to represent a multibillion dollar industry. On the dental side, bisphosphonates remain part of the consciousness of oral healthcare providers not because of their success in medicine but because of infamous side effects and the potential for morbidity.

How bisphosphonates work

The mechanism of action of all bisphosphonates is to inhibit bone resorption (osteoclastic activity) by attaching to hydroxyapatite binding sites on bony surfaces, especially surfaces undergoing active resorption. Bisphosphonates are released when osteoclasts resorb bone containing a bisphosphonate, and this impairs the ability of the osteoclasts to produce the protons necessary for continued bone resorption. Bisphosphonates further reduce osteoclastic activity by decreasing osteoclast progenitor development and recruitment as well as promoting osteoclast programmed cell death (apoptosis). The end result is reestablishment of the balance between bone formation and resorption and, over time, an increase in bone mass.

Bisphosphonates appear to have a beneficial effect on osteoblasts in addition to their inhibitory effect on osteoclasts. In a murine study of glucocorticoid-induced osteoporosis, bisphosphonates prevented osteoblast and osteocyte apoptosis. This mechanism facilitates activation of protein kinases, further accelerating the process toward increased bone mineral density.
A third mechanism of action of bisphosphonates is their antiangiogenic effect. The creation of new blood vessels (i.e., neoangiogenesis) in cancerous tissue plays a critical role in the growth and spread of tumor cells. Numerous studies on solid tumors have shown that bisphosphonates inhibit tumor angiogenesis, the differentiation and recruitment of endothelial progenitor cells, and the differentiation of myeloid cells into tumor-associated macrophages.

This antiangiogenic effect may be a key driver in the development of bisphosphonate-related osteonecrosis of the jaw (BRONJ). Bisphosphonates tend to be highly concentrated in the jaws rather than in other skeletal sites because they preferentially deposit in bones with high turnover rates (sites of significant remodeling). Another characteristic distinguishing the jaws from other bones is the type of ossification. The mandible and maxilla have an intramembranous ossification, unlike vertebrae and long bones, which have an endochondral ossification. The mandible is a common site for BRONJ specifically because of its density and low vascularity, which, when combined with injury, create an area with diminished ability to heal.

Not all bisphosphonates are created equally
While all bisphosphonates have a similar structure, the different radicals at R₁ and R₂ determine their individual characteristics. The common bisphosphonates and their associated side chains are shown in Table 1. In particular, bisphosphonates with a nitrogen side chain (alendronate, ibandronate, pamidronate, risedronate, and zoledronate) are much more potent than etidronate and those with a chloride side chain at the R₂ site (clodronate and tiludronate). This potency is often described as their antiresorptive effect on bone. As etidronate was the first available molecule in this drug class, it was assigned the antiresorptive potency of 1, and all bisphosphonates since are measured relative to etidronate (Table 2).

The concept of relative antiresorptive potency is particularly important in understanding both the intended effects and the side effects of these medications. In 2003 and 2004, there were several reports of osteonecrosis of the jaw in cancer patients receiving chronic intravenous bisphosphonates. The reports associated pamidronate and zoledronate specifically with osteonecrosis of the jaw, given their high relative antiresorptive potency and the fact that they are both intravenous formulations. In most cases, less than 5% of an orally administered bisphosphonate dose is absorbed due to the negative charge that hampers transport across the lipophilic cell membrane of the small intestine. To improve this bioavailability, agents such as pamidronate and zoledronate were formulated as parenteral medications, so that 100% of their dose is delivered directly to the systemic circulation. Pamidronate became available in the United States in 1991, while zoledronate did not become available until 2002. Intravenous etidronate is no longer available in the United States.

Origins of BRONJ
Both pamidronate and zoledronate were initially indicated for the treatment of hypercalcemia of malignancy. As a result of these BRONJ cases, the labeling of these products was updated in 2004 to include precautions about BRONJ. Given the heightened awareness around this adverse effect, many regulatory boards began to develop guidelines to

---

Table 1. Common bisphosphonates.

<table>
<thead>
<tr>
<th>Type</th>
<th>Radical</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R₁</td>
</tr>
<tr>
<td>Simple bisphosphonates</td>
<td></td>
</tr>
<tr>
<td>Clodronate</td>
<td>–Cl</td>
</tr>
<tr>
<td>Etidronate</td>
<td>–CH₃</td>
</tr>
<tr>
<td>Tiludronate</td>
<td>–H</td>
</tr>
<tr>
<td>Nitrogen-containing bisphosphonates</td>
<td></td>
</tr>
<tr>
<td>Alendronate</td>
<td>–OH</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>–OH</td>
</tr>
<tr>
<td>Pamidronate</td>
<td>–OH</td>
</tr>
<tr>
<td>Risedronate</td>
<td>–OH</td>
</tr>
<tr>
<td>Zoledronate</td>
<td>–OH</td>
</tr>
</tbody>
</table>

Table 2. Relative antiresorptive potencies of bisphosphonates.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Examples</th>
<th>Relative antiresorptive potency</th>
<th>Route of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-nitrogen-</td>
<td>Etidronate (Didronel)</td>
<td>1</td>
<td>PO and IV</td>
</tr>
<tr>
<td>containing side</td>
<td>Clodronate (Bonefos)</td>
<td>1-10</td>
<td>PO</td>
</tr>
<tr>
<td>chain</td>
<td>Tiludronate (Skelide)</td>
<td>10</td>
<td>PO</td>
</tr>
<tr>
<td>Nitrogen-containing side chain</td>
<td>Pamidronate (Aredia)</td>
<td>100</td>
<td>IV</td>
</tr>
<tr>
<td></td>
<td>Alendronate (Fosamax)</td>
<td>100-1000</td>
<td>PO</td>
</tr>
<tr>
<td></td>
<td>Risedronate (Actonel)</td>
<td>1000-10,000</td>
<td>PO</td>
</tr>
<tr>
<td></td>
<td>Ibandronate (Boniva)</td>
<td>1000-10,000</td>
<td>PO</td>
</tr>
<tr>
<td></td>
<td>Zoledronate (Zometa, Reclast)</td>
<td>&gt; 10,000</td>
<td>IV</td>
</tr>
</tbody>
</table>

Abbreviations: IV, intravenous; PO, oral.
help oral healthcare providers mitigate or avoid this effect in high-risk patients.\textsuperscript{27-32} Task forces were created, practice recommendations were published, and a formal definition of BRONJ was agreed upon: “an area of exposed bone in the maxillofacial region that did not heal within 8 weeks after identification by a healthcare provider, in a patient who was receiving or had been exposed to a bisphosphonate and had not had radiation therapy to the craniofacial region.”\textsuperscript{29} Unfortunately, many of these recommendations lacked consensus, and some of the original recommendations to withhold bisphosphonates for varying periods of time prior to dental surgery did not make sense given their long half-lives and relative permanency of embedment in skeletal bone (eg, the half-life of alendronate exceeds 10 years).

The other challenge during this period of heightened awareness about this side effect of the bisphosphonates involved case reports that included patients with variable medical histories, demographics, doses, and lengths of exposure to the different bisphosphonates. In other words, the medical and dental literature saw a proliferation of reports that began to delineate risk factors for identifying patients at highest risk for the development of BRONJ, but the practicing oral healthcare provider still struggled with explicit guidance on how to manage patients who were currently receiving bisphosphonates or how to formulate treatment plans for patients who were starting to take bisphosphonates. The American Dental Association provides a resource for current information on this important subject.\textsuperscript{34}

At present, the following are known risk factors for developing BRONJ: concomitant therapy with steroids, chemotherapy, and intravenous bisphosphonates (in a few instances, after short dosing); chemotherapy; immunotherapy; or other cancer treatment regimens; dental extraction; infectious disease; trauma; head and neck radiotherapy; female sex; coagulopathies; periodontal disease; bony exostosis; previous invasive dental procedures; dental prostheses; arthritis; blood dyscrasias; vascular disorders; alcohol abuse; smoking; and malnutrition.\textsuperscript{27-32}

**What is the real risk?**

Lost in this conflagration of concern was an accurate understanding of the true denominator: What are the actual incidence and prevalence of BRONJ? Kuhl et al reviewed 23 studies on the use of zoledronate and reported an incidence of BRONJ equal to 0%-11.5% in therapies up to 1 year and 0%-27.5% in therapies lasting from 1 to 4 years.\textsuperscript{36} The incidence of BRONJ after dental extractions has been reported to range from 1% to 11% in breast cancer patients, 3% to 17% in multiple myeloma patients, and 3% to 18% in prostate cancer patients.\textsuperscript{38-39} In another study to determine the prevalence of BRONJ, involving nearly 14,000 patients who had received chronic oral bisphosphonate therapy, only 9 cases of BRONJ were identified; there was a minimal prevalence of 1 in 952 respondents (0.10%) or 1 in 1537 in the target population (0.07%).\textsuperscript{39}

While many of these ranges are wide, in almost all cases where risk factors are minimal, the likelihood of developing BRONJ is also minimal and probably approaches zero.\textsuperscript{40} As patients accumulate additional risk factors, however, the likelihood of developing BRONJ increases.

Regardless of the dental risk, the overall medical benefit of bisphosphonates is often overlooked. Core registration and extension studies continue to demonstrate the overwhelming efficacy of these agents in treating osteoporosis, a disease characterized by reduced bone mass and increased skeletal fragility; osteoporosis affects 10 million Americans, and another 34 million are at risk.\textsuperscript{41} In fact, the American Academy of Orthopaedic Surgeons consistently ranks bisphosphonates as the recommended pharmacologic agents to treat osteoporosis and reduce fracture risk, assigning them an “A” level of evidence since there is “convincing evidence of antifracture efficacy.” This evidence is consistent in all areas of fracture risk from vertebral to hip to nonvertebral fractures (osteoporosis fractures exclusive of those of the spine).\textsuperscript{42}

In other words, the significant benefits of bisphosphonate treatment far exceed the potential risks of developing BRONJ.

**Where do we go from here?**

Professional organizations as well as international work groups continue to publish guidelines and recommendations on the management of patients with suspected or confirmed BRONJ.\textsuperscript{6,43-44} The term BRONJ has been updated to medication-related osteonecrosis of the jaw (MRONJ), given recent reports of drug-induced osteonecrosis of the jaw by nonbisphosphonate medications.\textsuperscript{45-50} General awareness among dental and medical professionals alike should lead to improved awareness of risk factors, which may be evident by the decreasing number of published case reports. Still, the number of patients receiving bisphosphonates and other antiangiogenic and antiresorptive agents such as denosumab is rising, and it is likely clinicians will encounter additional potential risk factors for MRONJ, especially as research expands into the genomic realm.

In the meantime, MRONJ-expert recommendations trend toward proceeding with most dental treatments with little to no modification in osteoporotic patients who take bisphosphonates.\textsuperscript{5}

A recent article summarized the prevalence of MRONJ as up to 0.01% in patients receiving oral bisphosphonates, 12% in patients receiving intravenous bisphosphonates, and 16% in patients receiving a combination of bisphosphonates and antiangiogenics.\textsuperscript{37} On balance, the benefits of bisphosphonate therapy in most cases outweigh the relatively low risk of adverse effects.

**Author information**

Dr Goodchild is the director of clinical affairs, Premier Dental Products Company, Plymouth Meeting, Pennsylvania; an associate clinical professor, Department of Diagnostic Sciences, Creighton University School of Dentistry, Omaha, Nebraska; an adjunct assistant professor, Department of Diagnostic Sciences, Rutgers School of Dental Medicine, Newark, New Jersey; and in private practice in Havertown, Pennsylvania. Dr Donaldson is a senior executive director, Vizient Pharmacy Advisory Solutions, Irving, Texas; a clinical professor, Skaggs School of Pharmacy, University of Montana, Missoula; and an adjunct professor, Faculty of Dentistry, University of British Columbia, Vancouver, Canada.

**Disclaimer**

The authors report no potential conflicts of interest pertaining to any of the products or companies discussed in this column. The views expressed in this column are those of the authors and do not necessarily reflect those of Creighton.
University School of Dentistry, Premier Dental Products Company, or Vizient, Inc.

References


12. Ginoza E, Inoue M, Hanahan D. An amino-bisphospho-


14. Vettraino JD, Lambers ME, van Nimwegen M, et al. Zole-
dronic acid impairs myeloid differentiation to tumour-as-


17. El-Rabbany M, Syro A, Lam DK, Shah PS, Azarpazhooh A. Effectiveness of treatments for medication-related osteonecrosis of the jaw: a systematic review and meta-

18. Van Arken HH, Anguille S, Willenzen Y, Smits EL, Van Tendelou VF. Bisphosphonates for cancer treatment: mecha-

19. Watts NB. Treatment of osteoporosis with bisphospho-
nates. Endocrinol Metab Clin North Am. 1998;27(2):419-

20. Ruggiero SL, Mehnotra B, Rosenberg TJ, Engroff SL. Osteo-
necrosis of the jaws associated with the use of bisphos-


22. Migliorati CA. Bisphosphonates [sic] and oral cavity avas-


24. Marx RE. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidem-


26. Novartis Pharmaceuticals Corporation. Are dia (pa-


28. Barker K, Rogers S. Bisphosphonate-associated osteone-
crosis of the jaws: a guide for the general dental practitio-

29. American Dental Association Council on Scientific Affairs. Dental management of patients receiving oral bisphos-

30. Pickett FA; American Academy of Oral Medicine. Bisphos-

31. Ruggiero S, Fantasia J, Carlson E. Bisphosphonate-relat-
ed osteonecrosis of the jaws associated with the use of bisphos-


33. Lo JC, O’Ryan FS, Gordon NP, et al. Prevalence of osteone-
crosis of the jaw in patients with oral bisphosphonate expo-


36. Boonyaparkorn T, Schirm E, Reichart PA, Sturm I, Massen-


crosis of the jaw in patients with oral bisphosphonate ex-


43. Rosella D, Papi P, Giardino R, et al. Medication-related osteo-

44. Ruggiero SL, Dobson TB, Fantasia J, et al. American Asso-
ciation of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw—2014 up-


46. Baroni R, Ferrari S, Russell RG. Denosumab and bisphos-


48. Henien M, Carey B, Hulland E, Sproat C, Patel V. Methotrex-