Bisphosphonates in the Treatment of Osteoporosis

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KEYWORDS

• Bisphosphonates • Osteoporosis • Long-term safety • Osteonecrosis of the jaw
• Atypical femur fractures • Atrial fibrillation • Esophageal cancer • Drug holidays

KEY POINTS

- Bisphosphonates are popular and effective for the treatment of osteoporosis.
- Since their initial introduction in the United States in 1995, questions have been raised about their association with possible uncommon side effects such as esophageal cancer, atrial fibrillation, musculoskeletal pain, osteonecrosis of the jaw, and atypical fractures.
- Because there seems to be some lingering antifracture benefit when treatment is stopped, "drug holidays" should be offered to most patients on long-term bisphosphonate therapy.
- The duration of treatment and the length of the holiday should be individualized based on fracture risk and the binding affinity of the particular bisphosphonate used.
- The benefits of treatment outweigh the risks for most patients with osteoporosis.

INTRODUCTION

Bisphosphonates are agents that share a common chemical structure, characterized by 2 phosphonic acids joined to a carbon along with 2 side chains designated R^1 and R^2, which influence the binding affinity and antiresorptive potency of the agent (**Fig. 1**).[1] This structure causes these compounds to bind avidly to hydroxyapatite crystals on bone surfaces, particularly at sites of active bone remodeling, which resulted in the use of these agents initially for nuclear bone scintigraphy. In the late 1960s, they began to be used as therapeutic agents for the treatment of a variety of metabolic bone diseases such as heterotopic ossification, fibrous dysplasia, osteogenesis imperfecta, Paget disease of bone, hypercalcemia, bone loss, destructive arthropathy, and skeletal involvement with malignancy.

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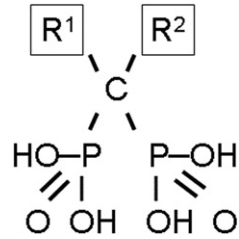

Fig. 1. Structure of pyrophosphate and germinal bisphosphonates. (*From* Watts NB. Bisphosphonate treatment for postmenopausal osteoporosis. In: Avioli L, editor. The osteoporotic syndrome. 4th edition. San Diego: Academic Press; 2000; with permission.)

PHARMACOLOGY, PHARMACOKINETICS, AND MECHANISM OF ACTION

Bisphosphonates can be taken by mouth or given intravenously. These agents are poorly absorbed when taken orally; less than 1% of an orally administered dose is absorbed under ideal conditions, and little or none under less than ideal situations. Therefore, they must be taken after a prolonged fast, with water only, followed by at least 30 minutes with nothing else by mouth to allow for adequate absorption. Atelvia, which is risedronate in a delayed-release formulation, is taken immediately following breakfast. About half of the absorbed dose binds to bone surfaces, mostly avidly at sites of active remodeling, and the other half is rapidly excreted by the kidneys.

The 4 bisphosphonates currently in clinical use for the treatment of osteoporosis are nitrogen-containing and differ in the strength for binding to bone (**Table 1**). The rank order for binding affinity is zoledronate > alendronate > ibandronate > risedronate.[2] Higher-affinity bisphosphonates will bind avidly to the bone surface but will spread through bone more slowly, whereas lower-affinity agents with be distributed more widely through the bone but have a shorter residence time in bone if treatment is stopped.[2]

Bisphosphonates reduce osteoclastic bone resorption by entering the osteoclast and causing loss or resorptive function as well as accelerating apoptosis by interfering with protein prenylation via inhibiting farnesyl pyrophosphate synthase, an enzyme in the HMG-CoA reductase pathway.[2,3] The rank order of potency for inhibiting farnesyl pyrophosphate synthase is zoledronate > risedronate >> ibandronate > alendronate.[2,3] The net result is a rapid and substantial decrease in bone turnover markers that is dose

Table 1
Structures of some of the bisphosphonates in clinical use

	R^1	R^2
Non–Nitrogen-Containing Compounds		
Etidronate	OH	CH_3
Clodronate	Cl	Cl
Tiludronate	H	SC_6H_3Cl
Nitrogen-Containing Compounds		
Pamidronate	OH	$CH_2CH_2NH_2$
Alendronate	OH	$CH_2CH_2CH_2NH_2$
Risedronate	OH	CH_2-3-pyridinyl
Zoledronate	OH	$CH_2C_3N_2H_3$

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