CE

Bisphosphonates and Atypical Femoral Fractures

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ABSTRACT

Bisphosphonates are frequently prescribed for osteoporosis, with more than 14 million prescriptions dispensed yearly in the United States. They have demonstrated increases in bone mineral density and reduction in vertebral and nonvertebral fractures for osteoporosis. However, 1 uncommon side effect associated with this class of medication is atypical femoral fractures located in the midshaft of the femur and associated with minimal or no trauma. This article outlines the epidemiology, pharmacology, definitions, physiology, and pathogenesis regarding these fractures. In addition, specific treatment and prevention strategies that nurse practitioners can utilize are discussed.

Keywords: atypical femoral fractures, bisphosphonates, etiology, osteoporosis

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In compliance with national ethical guidelines, the author reports no relationships with business or industry that would pose a conflict of interest.

Bisphosphonates are a frequently prescribed drug class for osteoporosis, with 14.7 million prescriptions for oral bisphosphonates dispensed in the United States in 2012 alone. Bisphosphonates began to be widely distributed in the mid-1990s after several clinical trials of alendronate of less than 5 years outlined an increase in bone mineral density (BMD) as well as a reduction in both vertebral and nonvertebral fractures for osteoporosis (BMD < -2.5). Bisphosphonates have not demonstrated significant fracture reductions in persons with osteopenia (BMD ≥ -2.5).[1]

Since the mid-1990s, long-term data have become available regarding the efficacy and potential adverse sequellae related to this class of medications. Although the short-term use of bisphosphonates has been shown to reduce fracture risk, the interpretation of the data is complicated by issues involving adherence, diagnostic coding, follow-up, and ethical issues that precluded placebo-treated controls once efficacy was established. No comparative trials between various bisphosphonates have been conducted nor are they ever likely to be conducted. The requisite prospective clinical trials that could show a causal link between

This CE learning activity is designed to augment the knowledge, skills, and attitudes of nurse practitioners and their understanding of bisphosphonates and the risk of atypical femoral fractures (AFFs).

At the conclusion of this activity, the participant will be able to:

A. Describe the risks associated with long-term bisphosphonate use
B. Discuss pharmacology/pathogenesis of AFFs
C. Plan appropriate treatment and prevention strategies regarding AFFs

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bisphosphonates and atypical femoral fractures (AFFs) are not likely to be conducted, and, thus, complete consensus has not been reached among providers.

One of the uncommon effects associated with long-term use of bisphosphonates is AFFs. These unusual fractures, located in the midshaft of the femur, are associated with minimal trauma and have distinctive features and clinical presentation that are not typical in osteoporosis-related fractures. There are no known publications to date in the nursing literature regarding these fractures. This article addresses AFFs, including epidemiology, pharmacology, definition, bone physiology, pathogenesis, delayed healing, management, and prevention.

EPIDEMIOLOGY OF AFFs

The first occurrences of bisphosphonate-related AFFs were reported in 2005.[2] This was followed by many reports of similar fractures involving the subtrochanteric, midshaft, and distal third of the femur, with the term *atypical femoral fracture* being coined in 2008.[3] Thus, the association between bisphosphonate exposure and AFFs was established in conjunction with the growing case series reports.[3,4] Beginning in 2003, there have also been occurrences of medication-related osteonecrosis of the jaw in association with bisphosphonate exposure.[5] In addition, reports have been published of bisphosphonate-related atraumatic or low-energy fractures of the tibial diaphysis, clavicle, fibula, metatarsal, humerus, pelvis, and ulna.[2,3,6–9]

In response to the emerging reports of atypical fractures related to bisphosphonates, in 2010 the United States Food and Drug Administration added language to the "Warnings and Precautions" section of all bisphosphonate drugs. This warning in part includes the recommendation for providers to evaluate any patient who presents with "new thigh or groin pain" and to consider "periodic reevaluation" of whether to continue bisphosphonates for those persons prescribed the drug for longer than 5 years.[10]

PHARMACOLOGY AND MECHANISMS OF ACTION

Bisphosphonates have a selective strong affinity for bone tissue, increase BMD, and reduce markers of bone turnover. This is accomplished through osteoclast apoptosis (cell death) and bone turnover suppression. Despite an increase in BMD, bisphosphonates do not cause a net buildup of bone in the skeleton.

Bisphosphonates are categorized into 2 subtypes: non—nitrogen containing and nitrogen containing. The older non—nitrogen-containing bisphosphonates are metabolized to analogs of adenosine triphosphate and are less potent. The newer nitrogen-containing bisphosphonates are not metabolized, are excreted unchanged via the kidney, and act to inhibit farnesyl pyrophosphate synthetase (a cholesterol synthesis enzyme) (Table). These agents are very potent, increasing the antiresorptive potency of the drug with a tendency toward more adverse side effects. They prevent the activation of key proteins involved in many biological processes, and are necessary for bone-resorbing actions and osteoclast survival. Alendronate and risedronate are the most commonly prescribed bisphosphonates.

Only 1% of bisphosphonates are bioavailable when ingested orally. They are cleared from the plasma rapidly. Fifty percent is deposited in bone and the remainder quickly excreted in the urine. They bind to bone surface at active remodeling areas and get internalized into osteoclasts through endocytosis, being engulfed into the cell.

Bisphosphonates have a very long duration of action, with half-life estimates of alendronate skeletal binding for greater than 10 years. Recovery of bone turnover after withdrawal is altered, with biomarkers of remodeling remaining significantly lower in women who were prescribed the medications for 10 years compared with those who were prescribed it for 5 years and were taken off for another 5 years. Recovery of bone remodeling after bisphosphonates are stopped appears to be dose, time, and drug dependent.[10,11]

Table. Bisphosphonates Commonly Used in the United States

Generic Name	Brand Name	Nitrogen Containing
Alendronate	Fosamax	Yes
Ibandronate	Boniva	Yes
Pamidronate	Aredia	Yes
Risedronate	Actonel	Yes
Zoledronate	Zometa, Reclast	Yes