

FPIN's Clinical Inquiries

Risks of Bisphosphonate Use

MOLLIE ASHE SCOTT, PharmD, *University of North Carolina Eshelman School of Pharmacy, Asheville, North Carolina*

LINDSY MEADOWCRAFT, PharmD, *South Carolina College of Pharmacy, Charleston, South Carolina*

DEBBIE SKOLNIK, MLS, *Mountain Area Health Education Center, Asheville, North Carolina*

Clinical Inquiries provides answers to questions submitted by practicing family physicians to the Family Physicians Inquiries Network (FPIN). Members of the network select questions based on their relevance to family medicine. Answers are drawn from an approved set of evidence-based resources and undergo peer review. The strength of recommendations and the level of evidence for individual studies are rated using criteria developed by the Evidence-Based Medicine Working Group (<http://www.cebm.net/?o=1025>).

The complete database of evidence-based questions and answers is copyrighted by FPIN. If interested in submitting questions or writing answers for this series, go to <http://www.fpin.org> or email: questions@fpin.org.

A collection of FPIN's Clinical Inquiries published in *AFP* is available at <http://www.aafp.org/afp/fpin>.

Clinical Question

What are the risks of bisphosphonate use?

Evidence-Based Answer

Bisphosphonates are associated with a small risk of atypical femoral shaft fractures, which increases with duration of use. (Strength of Recommendation [SOR]: B, based on case-control and cohort studies.) Bisphosphonates are associated with a small risk of osteonecrosis of the jaw, which is more common in patients who are older, female, or have poor dental hygiene or cancer. (SOR: B, based on systematic reviews.) Alendronate (Fosamax) and risedronate (Actonel) may cause bone and joint pain. (SOR: C, based on case reports.) Physicians should discontinue bisphosphonate therapy in patients who have had a femoral shaft fracture or osteonecrosis of the jaw, and should consider discontinuing bisphosphonate therapy after three to five years in patients with low fracture risk. (SOR: C, based on expert opinion.)

Evidence Summary

FRACTURES

Atypical femoral shaft fractures occur in the subtrochanteric or diaphyseal region and are associated with minimal trauma. A nested case-control study from Canada matched 716 women 79 to 88 years of age who sustained a subtrochanteric or femoral shaft fracture after receiving bisphosphonate therapy with 3,580 control patients who did not have fractures.¹ Compared with transient use (less than 100 days), bisphosphonate use for five years or longer was associated with an increased risk of atypical fractures (adjusted odds ratio = 2.74; 95% confidence interval [CI], 1.25 to 6.02). The authors evaluated prescription data and found that of 52,595 women receiving

bisphosphonates for more than five years, only 71 (0.13%) sustained an atypical fracture.

A case-control study retrospectively reviewed the medical records of 477 patients older than 50 years who were treated in a Swiss hospital for subtrochanteric or femoral shaft fracture.² Fractures were categorized as atypical (transverse or short oblique; n = 39) or classic (spiral, wedge, segmental, or complex irregular; n = 438). Researchers compared bisphosphonate use and duration of therapy in these groups and in 200 patients older than 50 years who did not have fractures. Bisphosphonate use among the atypical, classic, and no-fracture groups was 82.1%, 6.4%, and 11.5%, respectively.

After adjusting for sex and for corticosteroid and vitamin D use, the use of bisphosphonates was associated with an odds ratio of 49.7 for an atypical fracture compared with the no-fracture group (95% CI, 15.9 to 155.1). However, the odds ratio for a classic fracture was 0.5 (95% CI, 0.3 to 0.9), suggesting a 50% reduction in these types of fractures in women receiving bisphosphonates. The odds ratio for atypical vs. classic fracture risk increased with the duration of bisphosphonate treatment; the odds ratio for less than two years of use was 35.1 (95% CI, 10.0 to 123.6), for two to five years was 46.9 (95% CI, 14.2 to 154.4), for five to nine years was 117.1 (95% CI, 34.2 to 401.7), and for more than nine years was 175 (95% CI, 30 to 1,028). Overall fracture incidence rates were low (357 classic and 32 atypical fractures per 1 million person-years). The incidence of classic fractures over 12 years was stable, but the incidence of atypical fractures increased 10.7% per year (95% CI, 0.4% to 20.3%).²

In 2008, case-control and cohort studies were conducted with 1.5 million Swedish ►

Clinical Inquiries

women older than 50 years, 83,311 of whom were receiving bisphosphonates.³ Femoral fractures were identified in 12,777, and 59 of these fractures were atypical. The authors calculated that the relative risk for atypical fracture in women receiving bisphosphonates was 47.5 (95% CI, 25.6 to 87.3). However, the absolute risk was low, with a number needed to harm (NNH) of 2,000 (95% CI, 1,429 to 2,500). The risk was lowest in women with less than one year of use (NNH = 5,000) and highest for those with more than two years of use (NNH = 1,250).

OSTEONECROSIS OF THE JAW

The estimated incidence of osteonecrosis of the jaw is 1 to 10 per 100,000 patient-treatment years.⁴ Nonsystematic reviews suggest that it occurs in up to 20% of patients with cancer who receive intravenous bisphosphonates, but in only about 0.04% of patients with osteoporosis who receive oral bisphosphonates.^{4,5}

A blinded review of adverse events from five randomized controlled trials (11,608 participants) comparing zoledronic acid (Reclast) with placebo or another bisphosphonate found one case of osteonecrosis in the zoledronic acid group and one in the control group.⁶ A 2007 systematic review of eight case reports or case series and three retrospective studies included 26 patients with osteonecrosis of the jaw who were taking bisphosphonates for osteoporosis.⁷ The bisphosphonates were oral alendronate (88%), oral risedronate (4%), intravenous pamidronate (4%), and a combination of oral alendronate and intravenous zoledronic acid (4%). Patients with osteonecrosis of the jaw were more likely to be older than 60 years (78%), to be women (77%), and to have had recent dental surgery or trauma (80%).

BONE AND MUSCLE PAIN

Alendronate and risedronate may cause musculoskeletal pain. In a seven-year postmarketing survey of serious adverse events reported to the U.S. Food and Drug Administration (FDA), 118 patients developed severe bone, joint, or muscle pain after taking oral alendronate.⁸ The median time to pain onset was 14 days (range = 1 to 1,560 days). Of 83 patients for whom complete information was available, 55 (66%) had pain relief after discontinuing alendronate, and nine (11%) had recurrent pain after restarting the drug. Most patients had gradual improvement after discontinuing the medication. From 1998 to 2003, the FDA received six reports of musculoskeletal pain in patients receiving risedronate.⁸

Recommendations from Others

The FDA recommends discontinuing bisphosphonates in patients who have had a femoral shaft fracture.⁹ It also

recommends that physicians consider whether severe musculoskeletal pain is caused by bisphosphonate use.¹⁰

The American Dental Association recommends that patients on bisphosphonate therapy receive regular dental care to lower the risk of osteonecrosis of the jaw. It does not recommend modifying dental treatment because of bisphosphonate use, and notes that discontinuing bisphosphonates may not eliminate or reduce the risk of developing osteonecrosis.⁵

The National Osteoporosis Foundation recommends that all patients receiving bisphosphonates be reevaluated after three to five years.¹¹ Physicians may discontinue treatment in those with low fracture risk; however, they should consider continuing treatment with a bisphosphonate or alternative therapy beyond five years in patients with high fracture risk.

The authors thank Megan Fontana, PharmD, and Lisa Ray, MD, for assistance with the preparation of the manuscript.

Copyright Family Physicians Inquiries Network. Used with permission.

Address correspondence to Mollie Ashe Scott, PharmD, at mollie_scott@unc.edu. Reprints are not available from the authors.

Author disclosure: No relevant financial affiliations.

REFERENCES

1. Park-Wyllie LY, Mamdani MM, Juurlink DN, et al. Bisphosphonate use and the risk of subtrochanteric or femoral shaft fractures in older women. *JAMA*. 2011;305(8):783-789.
2. Meier RP, Perneger TV, Stern R, et al. Increasing occurrence of atypical femoral fractures associated with bisphosphonate use. *Arch Intern Med*. 2012;172(12):930-936.
3. Schilcher J, Michaélsson K, Aspenberg P. Bisphosphonate use and atypical fractures of the femoral shaft [published corrections appear in *N Engl J Med*. 2011;365(16):1551, and *N Engl J Med*. 2012;367(6):582]. *N Engl J Med*. 2011;364(18):1728-1737.
4. Khosla S, Burr D, Cauley J, et al. Bisphosphonate-associated osteonecrosis of the jaw. *J Bone Miner Res*. 2007;22(10):1479-1491.
5. Edwards BJ, Hellstein JW, Jacobsen PL, et al. Updated recommendations for managing the care of patients receiving oral bisphosphonate therapy [published correction appears in *J Am Dent Assoc*. 2009;140(5):522]. *J Am Dent Assoc*. 2008;139(12):1674-1677.
6. Grbic JT, Black DM, Lyles KW, et al. The incidence of osteonecrosis of the jaw in patients receiving 5 milligrams of zoledronic acid. *J Am Dent Assoc*. 2010;141(11):1365-1370.
7. Pazianas M, Miller P, Blumentals WA, et al. A review of the literature on osteonecrosis of the jaw in patients with osteoporosis treated with oral bisphosphonates. *Clin Ther*. 2007;29(8):1548-1558.
8. Wysowski DK, Chang JT. Alendronate and risedronate: reports of severe bone, joint, and muscle pain. *Arch Intern Med*. 2005;165(3):346-347.
9. U.S. Food and Drug Administration. Bisphosphonates (osteoporosis drugs): label change—atypical fractures update. <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm229244.htm>. Accessed December 19, 2012.
10. U.S. Food and Drug Administration. Information for healthcare professionals: bisphosphonates. <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124165.htm>. Accessed December 19, 2012.
11. National Osteoporosis Foundation. 2013 clinician's guide to the prevention and treatment of osteoporosis. <http://www.nof.org/hcp/resources/913>. Accessed April 30, 2013. ■