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Bone, Muscle, and Joint Problems with Bisphosphonates

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Background

The bisphosphonates are a group of products that are effective in the prevention and treatment of postmenopausal and glucocorticoid-induced osteoporosis and also Paget’s disease. They increase bone density by binding to the surfaces of bones and slow down osteoclastic activity, thereby facilitating osteoblastic effectiveness. Alendronate (Fosamax) and risedronate (Actonel) are commonly prescribed bisphosphonate agents. The most common side effect of the bisphosphonates is gastrointestinal upset. This is often dose-related.1-3

Post-marketing surveillance data from several countries are revealing severe bone, joint, and muscle pain associated with these agents, specifically alendronate and risedronate.4-7

Reported Events

Since the marketing of Fosamax in the US beginning September 1995 up to November 2002, there have been 118 reports of severe bone, joint, and/or muscle pain in patients. Ninety-six percent of these events occurred in women. Of those cases for which sufficient information was provided, 74% occurred at a daily dose of 10 mg and 18% occurred with a once-weekly dosage of 70 mg. Pain onset ranged from the same day to 52 months with an average of 14 days from therapy start. In some patients, pain initiated in one site then migrated and became diffuse. Pain was severe enough to require bedrest, walkers, or crutches and resulted in inability to perform usual activities for some patients. Opioids, ketorolac (Toradol), or other agents were used to treat the pain. In 66% of the patients, Fosamax was discontinued; some experienced immediate relief but most had gradual improvement. Eleven percent of the patients for whom therapy was discontinued redeveloped pain after therapy restart.4

Post-marketing surveillance data for Actonel from its marketing in September 1998 through June 2003 have revealed six severe cases of bone, joint, or muscle pain. Specific demographic, epidemiologic, or dosage data have not been published at this time.4

The Australian Adverse Drug Reactions Advisory Committee has received 61 reports of musculoskeletal adverse events since the 1996 marketing of Fosamax there. Of these 61 cases, 35 reported muscle pain, 29 identified joint pain, six were associated with bone pain, and ten cases had mixed muscle and joint pain. Onset of pain ranged from the start day to over one year of therapy. Pain recurred in 13% of those re-challenged with the drug.5

Data from the Canadian Adverse Drug Reaction Monitoring Program for the time period of December 1995 to January 1998 identified two cases of alendronate-associated musculoskeletal pain from a total of 138 reports. One case involved exacerbation of rheumatoid arthritis with accompanying gastrointestinal complaints in a 64 year old woman after receiving alendronate 10 mg daily for four weeks.6

In a study of alendronate-associated esophageal reaction incidence by Mackay et al, the researchers used a calculated incidence density for reporting events. In their study period nausea/vomiting incidence was 8.3, dyspepsia incidence was 11.3, abdominal pain incidence was 7.5, back pain incidence was 5.3, and joint pain incidence was 4.1.7

Commentary

These data suggest an association of bisphosphonate-related musculoskeletal pain. However, there is no specific baseline data on the incidence of existing musculoskeletal conditions in these patients. This makes the clinical significance of these observations difficult to determine. Furthermore, underreporting of these

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musculoskeletal adverse events may occur due to confusion of drug-related vs disease-related conditions such as pre-existing osteoporosis or osteoarthritis. It is interesting to note that in the therapy discontinuation cases mentioned above, pain reoccurred with bisphosphonate rechallenge in only 11 to 13% of recorded cases.4,5

Newly reported cases of musculoskeletal pain following initial or prolonged treatment with bisphosphonate agents should be checked. A bisphosphonate discontinuation trial may be initiated to potentially determine an association when other causes of pain have been ruled-out.

Other non-bisphosphonate agents that may be used for osteoporosis include estrogen replacement (based on the individual woman’s history and risk factors and used for the shortest period at the lowest possible dose), raloxifene (Evista), calcitonin (Miacalcin), and synthetic parathyroid hormone (Forteo). Adequate calcium and vitamin D are essential supplements but not adequate alone for treatment.1,2

Encourage reporting of suspected adverse drug events. To report adverse events in the US, call the FDA MEDWATCH program at 1-800-FDA-1088. The MEDWATCH program is also available on-line at www.fda.gov/medwatch. In Canada, call the Canadian Adverse Drug Reaction Monitoring Program at 1-866-234-2345. The Canadian adverse reaction reporting form can be found at: http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/adverse_e.pdf. It should be completed and faxed to 1-866-678-6789.

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References

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