Case Series

Alendronate-Induced Synovitis

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ABSTRACT. We describe 7 cases of synovitis or arthritis occurring after commencement of alendronate for treatment of osteoporosis. These were cases from our practice or notified to the New Zealand Pharmacovigilance Centre, Dunedin, New Zealand. There was no evidence of rheumatoid arthritis, pyrophosphate arthropathy, or seronegative arthritis in any patient. Symptoms recurred on rechallenge in 5 of the cases. We conclude alendronate should be considered as a possible cause of synovitis or polyarthritis in patients treated with it in the absence of any other pathology. (First Release Jan 15 2008; J Rheumatol 2008;35:537–8)

Key Indexing Terms:
ALENDRONATE SYNOVITIS ARTHRITIS ADVERSE DRUG REACTION

Bisphosphonates are drugs commonly used in the treatment of postmenopausal osteoporosis. Alendronate (Fosamax®, Merck & Co. Inc.) is a potent oral preparation licensed for prevention (5 mg daily) and treatment of postmenopausal osteoporosis (70 mg weekly or 10 mg daily)[1]. Oral bisphosphonates including alendronate commonly cause gastrointestinal disturbances[1-4] and also musculoskeletal pain[5]. Occurrence of a systemic inflammatory reaction with fever, flu-like symptoms, and elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) is recognized to occur, in some patients, after the initial dose of intravenous pamidronate. However, this does not usually occur after subsequent doses.

We review a series of patients with marked synovitis or polyarthritis induced by administration of alendronate. Patients were identified in 3 ways: from the New Zealand Pharmacovigilance Centre, using its Centre for Adverse Reactions Monitoring (CARM) spontaneous reporting database, from our clinical practice, and from personal communications after publication of our initial case report[6]. Details of the reaction were checked with the patient's general practitioner and the patient was reinterviewed when necessary.

CASE SERIES

Patient 1. A 69-year-old woman had been treated for osteoporosis with cyclical etidronate for 4 years. Within 24 hours of commencing alendronate 70 mg weekly, she developed synovitis in her right wrist and within 72 hours developed an acute carpal tunnel syndrome. At surgery, fluid was found in the carpal tunnel, but no organisms or crystals were seen. There was no evidence of pyrophosphate arthropathy. Laboratory tests included a consistently normal CRP and ESR, calcium 2.41 mmol/l, ferritin 39 µg/l, uric acid 0.3 mmol/l, antinuclear antibody titer 1/80, and negative extractable nuclear antigen, double-stranded DNA and rheumatoid factor. Alendronate was restarted at 10 mg daily 5 months later, but she developed pain in multiple joints after 3 days. The symptoms recurred on rechallenge of 10 mg on alternate days. She recovered fully upon discontinuing alendronate.

Patient 2. A 58-year-old woman developed hot, red, swollen knees and headache within 3 weeks of starting alendronate 10 mg daily. The symptoms resolved when she discontinued the drug. When alendronate was reintroduced at 5 mg daily she developed a headache after 1 week, which resolved 3 days later, but after 4 weeks of taking the lower dose she again developed hot, red, swollen knees.

Patient 3. A 74-year-old woman developed an effusion in the left wrist and then 1 knee and 1 elbow after starting 70 mg alendronate weekly. There was a severe recurrence after a further dose and alendronate was discontinued.

Patient 4. A 56-year-old woman developed synovitis in both knees and edema of the lower legs 1 week after a first 70-mg dose of alendronate. She was rechallenged a week later with a more severe recurrence of symptoms and an elevation in CRP to 18 mg/l with normal ESR. She recovered over 3 weeks.

Patient 5. A 73-year-old woman commenced alendronate 10 mg daily but developed widespread joint pain and swelling of the small joints in the hands. She also developed diarrhea and nausea. The symptoms resolved within a few days of stopping the drug. A rechallenge resulted in a return of the joint symptoms such that she refused any further treatment. She had no history of previous joint problems or pyrophosphate arthropathy.

Patient 6. A 69-year-old woman commenced alendronate 70 mg weekly for osteoporosis confirmed by dual-energy x-ray absorptiometry, and a wrist fracture. She developed an acutely swollen knee with a large effusion within days. Withdrawal of alendronate resulted in rapid resolution of the knee effusion. No further bisphosphonate treatment was tried and she was subsequently treated with raloxifene, vitamin D, and calcium. She had no evidence of pyrophosphate arthropathy.

Patient 7. A 66-year-old woman developed bilateral hand and wrist swelling 1 day after taking her second weekly dose of alendronate 70 mg. The left wrist swelling resolved, but the right remained swollen for about 2 weeks with diffuse swelling and tenderness, especially over the wrist and

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metacarpophalangeal joints. Her ESR was 45 mm/h and CRP 18. She improved with a course of prednisone, but had not fully recovered 1 month later.

DISCUSSION

Alendronate, like other bisphosphonates, has a high affinity for mineralized bone and binds to calcium ions via negative charges on the 2 phosphate groups found on the bisphosphonate nucleus. It is taken up by osteoclasts during normal bone resorption. The nitrogen-containing bisphosphonates (pamidronate, alendronate, risedronate, and zoledronate) inhibit farnesyl pyrophosphate synthase, which is a key enzyme on the mevalonate pathway that leads to cholesterol synthesis. Loss of protein prenylation in early osteoclast precursors then blocks the development of osteoclasts. In contrast, non-nitrogen-containing bisphosphonates (etidronate and clodronate) cause osteoclast apoptosis via inhibition of ADP/ATP translocase[3]. It is not clear whether this difference may explain why some patients are intolerant of alendronate but are able to tolerate longterm etidronate.

The occurrence of a transient acute-phase response with fever, flu-like symptoms, and elevated ESR and CRP is well recognized, in some patients, after the initial dose of intravenous pamidronate, but not subsequent doses. This has been attributed to the release of proinflammatory cytokines. A similar response may also occur taking alendronate, with myalgia, malaise, and rarely fever[5]. In clinical trials there was a small increase in the number of patients developing muscle, bone, and joint pain compared with placebo[5]. Other inflammatory reactions reported include ocular inflammation[7,8], esophagitis, and gastritis[2].

An association between alendronate and synovitis was first noted in March 2003 by the Uppsala Monitoring Centre based on 8 reports in the database of the WHO Collaborating Centre for International Drug Monitoring[9].

There has been one published report of a case of severe myalgia and polyarthritis[10] and one of persistent polyarticular synovitis following the use of alendronate[11]. We previously reported case one of this series[6].

Evidence of rheumatoid arthritis, pyrophosphate arthropathy, or seronegative arthritis was sought and not found in the 3 patients identified in our clinical practice. Five of the 7 patients were rechallenged with a recurrence of symptoms. This strongly supports the premise that alendronate was the cause of the synovitis.

The purpose of our report is to highlight the potential adverse effect of synovitis induced by alendronate. With increasing use of this drug in the treatment and prevention of osteoporosis it is likely that more cases may arise. Alendronate should be considered as a possible cause of synovitis or polyarthritis in patients treated with this agent in the absence of any other pathology.

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