

Delayed Gastrointestinal Complications Associated with Alendronate: a Case Involving an Elderly Nursing Home Resident

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INTRODUCTION

Alendronate (Fosamax®) is an amino-bisphosphonate that binds to bone hydroxyapatite and inhibits osteoclast activity in bone resorption.¹ It is indicated for the treatment of Paget's disease, as well as for the prevention and treatment of osteoporosis in postmenopausal women. Alendronate can cause local irritation of the upper gastrointestinal mucosa leading to esophagitis, esophageal ulcers, and erosion. The product monograph² provides direction on proper administration to lessen the risk of esophageal injury. However, even when these directions are followed, esophageal injury is possible. This report describes a case of probable upper gastrointestinal damage in a very elderly patient who had been taking alendronate for more than 1 year.

CASE REPORT

A 94-year-old woman was admitted to a long-term care centre in December 1996 because of global deterioration in her condition. Her diagnoses included insulin-dependent diabetes mellitus, dyslipidemia, cognitive impairment, and decreased visual and auditory acuity; she had also fractured a rib during a recent episode of pneumonia. The family clearly indicated that they did not wish cardiopulmonary resuscitation under any circumstances and that they wanted the focus to be on "care and comfort".

On admission, the patient's medications consisted of insulin, pravastatin 20 mg daily, and alendronate 10 mg daily. During the admission conference, the potential

complications of the medications were discussed, as were the dubious benefits of pravastatin and alendronate for this particular patient. Both drugs had been started by the patient's family physician just prior to the admission. Neither pravastatin nor alendronate was on the facility's formulary, so the family was supplying both medications. Pravastatin was discontinued during the conference, but the family was reluctant to stop alendronate because of the recent rib fracture.

The clinical pharmacist discussed the proper administration of alendronate with the nursing staff who administered the medications, and an instruction sheet was posted on the wall beside the patient's bed. The head of the patient's bed was to be raised and her arms placed over a pillow on the feeding tray. Then the drug was to be given, at least 30 min before breakfast with a full glass of water, and the patient was to remain sitting upright until breakfast. No problems were encountered during the first year after admission. After that time, the patient gradually started to spit with increasing frequency, and she vomited occasionally. The spitting and vomiting were thought to represent a behavioural problem, as the patient was cognitively impaired and there was no previous history of dysphagia or esophageal disease. The problem was not discussed with the physician or the pharmacist. After the patient had lost 4.8 kg over 14 months, to reach a low of 39.3 kg, the issue was raised at the annual patient care conference. Her vomiting had become much worse and her glucose levels, as determined by glucometer, had dropped an average of 3.5 mmol/L, despite reduction in her insulin dosage. However, hematemesis had never occurred.

The family did not wish to have the patient admitted to hospital and refused investigation. Alendronate was stopped immediately, and the caregivers noticed that the frequency of vomiting declined within 3 weeks. By 8 weeks after discontinuation of alendronate, the vomiting had stopped. The patient's weight stabilized, and glucose levels increased by more than 8 mmol/L, such that adjustments to the insulin dosage were required. No other changes were made to the patient's medications or care plan during this period.

DISCUSSION

As with many case reports, where cause and effect cannot be established conclusively, it is not certain that alendronate was the cause of this patient's upper gastrointestinal distress. Because of the patient's cognitive impairment and the family's refusal of further investigation, a more definitive diagnosis based on endoscopy was not pursued. However, because the patient's vomiting lessened and eventually stopped altogether, and her weight and glucose levels improved after discontinuation of alendronate, this drug was suspected to have been the cause of the vomiting.

Bisphosphonates containing primary amino side chains, such as alendronate and pamidronate, have been shown to have a greater tendency to cause gastric damage than other bisphosphonates.^{3,4}

An animal study of alendronate suggested that gastrointestinal injuries result from the reflux of acidic gastric content containing alendronate, exacerbation of preexisting esophageal damage, or prolonged contact between the tablet and the esophagus.⁵ That study also showed that esophageal injury is less likely at a pH of 3.5 or higher, where alendronate is present predominantly as the sodium salt.⁵

Most of the human studies on the benefits and side effects of alendronate have involved people in their early 40s to their early 80s.^{3,6-16} There have been no published studies of alendronate use by people older than 85 years of age. Several case reports have associated alendronate with esophageal injury. Most describe symptoms occurring early in the course of therapy.¹⁷⁻¹⁹ De Groen and colleagues¹⁹ analyzed 199 cases of adverse esophageal effects reported to the manufacturer of alendronate through postmarketing surveillance. They found that, for 43 cases in which the time of onset of symptoms was reported, onset was within 1 month of initiating therapy in 39 and within 2 months in 42. In only 1 of 43 cases did esophageal symptoms develop more than 2 months after the patient started taking alendronate. However, Ryan and colleagues²⁰ reported a

case of severe esophagitis with stricture that developed after 10 months of therapy with alendronate. The patient in our case developed symptoms after more than 1 year of alendronate therapy.

Because frail elderly patients are more susceptible to the side effects of medications, it is prudent to weigh the benefits that they will gain from alendronate against the risk of upper gastrointestinal damage and bleeding. Also, patients with cognitive impairment who are receiving alendronate should be closely monitored for changes in appetite arising from gastrointestinal irritation. Cognitively impaired patients may be unable to verbalize their complaints, so behavioural changes may be the only indication of an adverse medication effect. Such changes may be small and could be mistaken for unrelated behavioural problems.

This report emphasizes that, even with proper administration, frail elderly patients may be at greater risk than younger patients for gastrointestinal complications caused by alendronate. The risks of alendronate use should be carefully weighed against the potential benefits before the drug is prescribed. If the decision is to use the drug, then there must be close monitoring for adverse gastrointestinal effects, including changes in appetite and weight loss, especially if the patient is unable to verbalize symptoms.

References

1. Breuil V, Cosman F, Stein L, Horbert W, Nieves J, Shen V, et al. Human osteoclast formation and activity in vitro: effects of alendronate. *J Bone Miner Res* 1998;13:1721-9.
2. Merck Frosst Canada & Co. Fosamax® (alendronate) product monograph. Kirkland (QC); 2000: Mar 20.
3. Graham DY, Malaty HM. Alendronate gastric ulcers. *Aliment Pharmacol Ther* 1999;13:515-9.
4. Blank MA, Ems BL, Gibson GW, Myers WR, Berman SK, Phipps RJ, et al. Nonclinical model for assessing gastric effects of bisphosphonates. *Dig Dis Sci* 1997;42:281-8.
5. Peter CP, Handt LK, Smith SM. Esophageal irritation due to alendronate sodium tablets: possible mechanisms. *Dig Dis Sci* 1998;43:1998-2002.
6. Hochberg MC, Ross PD, Black D, Cummings SR, Genant HK, Nevitt MC, et al. Larger increases in bone mineral density during alendronate therapy are associated with a lower risk of new vertebral fractures in women with postmenopausal osteoporosis. Fracture Intervention Trial Research Group. *Arthritis Rheum* 1999;42:1246-54.
7. Felsenberg D, Alenfeld F, Bock O, Hammermeister C, Gowan W. Placebo-controlled multicenter study of oral alendronate in postmenopausal osteoporotic women. FOSIT-Study-Group. Fosamax International Trial. *Maturitas* 1998;31:35-44.
8. Watts NB, Becker P. Alendronate increases spine and hip bone mineral density in women with postmenopausal osteoporosis who failed to respond to intermittent cyclical etidronate. *Bone* 1999;24:65-8.



9. Cummings SR, Black DM, Thompson DE, Applegate WB, Barrett-Connor E, Musliner TA, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. *JAMA* 1998;280:2077-82.
10. Saag KG, Emkey R, Schnitzer TJ, Brown JP, Hawkins F, Goemaere S, et al. Alendronate for the prevention and treatment of glucocorticoid-induced osteoporosis. Glucocorticoid-Induced Osteoporosis Intervention Study Group. *N Engl J Med* 1998;339:292-9.
11. Lanza F, Rack MF, Simon TJ, Lombardi A, Reyes R, Suryawanshi S. Effects of alendronate on gastric and duodenal mucosa. *Am J Gastroenterol* 1998;93:753-7.
12. McClung M, Clemmesen B, Daifotis A, Gilchrist NL, Eisman J, Weinstein RS, et al. Alendronate prevents postmenopausal bone loss in women without osteoporosis. A double-blind, randomized, controlled trial. Alendronate Osteoporosis Prevention Study Group. *Ann Intern Med* 1998;128:253-61.
13. Hosking D, Chilvers CE, Christiansen C, Ravn P, Wasnich R, Ross P, et al. Prevention of bone loss with alendronate in postmenopausal women under 60 years of age. Early Postmenopausal Intervention Cohort Study Group. *N Engl J Med* 1998;338:485-92.
14. Karpf DB, Shapiro DR, Seeman E, Ensrud KE, Johnston CC Jr, Adami S, et al. Prevention of nonvertebral fractures by alendronate. A meta-analysis. Alendronate Osteoporosis Treatment Study Groups. *JAMA* 1997;277:1159-64.
15. Bone HG, Downs RW Jr, Tucci JR, Harris ST, Weinstein RS, Licata AA, et al. Dose-response relationships for alendronate treatment in osteoporotic elderly women. Alendronate Elderly Osteoporosis Study Centers. *J Clin Endocrinol Metab* 1997;82:265-74.
16. Devogelaer JP, Broll H, Correa-Rotter R, Cumming DC, De Deuxchaisnes CN, Geusens P, et al. Oral alendronate induces progressive increases in bone mass of the spine, hip, and total body over 3 years in postmenopausal women with osteoporosis. *Bone* 1996;18:141-50.
17. Colina RE, Smith M, Kikendall JW, Wong RK. A new probable increasing cause of esophageal ulceration: alendronate. *Am J Gastroenterol* 1997;92:704-6.
18. Maconi G, Porro GB. Multiple ulcerative esophagitis caused by alendronate. *Am J Gastroenterol* 1995;90:1889-90.
19. De Groen PC, Lubbe DF, Hirsch LJ, Daifotis A, Stephenson W, Freedholm D, et al. Esophagitis associated with the use of alendronate. *N Engl J Med* 1996;335:1016-21.
20. Ryan JM, Kelsey P, Ryan BM, Mueller PR. Alendronate-induced esophagitis: case report of a recently recognized form of severe esophagitis with esophageal stricture — radiographic features. *Radiology* 1998;206:389-91.

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