Case Report

Ocular side effects of bisphosphonates

A case report and literature review

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Osteoporosis carries a high burden of illness, both for individual patients and society. In addition to substantial health care system costs, osteoporosis-associated fractures cause pain, disability, and increased risk of institutionalization. An estimated 50% of Canadian women older than 80 years of age meet diagnostic criteria for osteoporosis.[1]

Family physicians work with patients to prevent and treat osteoporosis on a daily basis. The current mainstay of treatment for osteoporosis is therapy with bisphosphonates, a class of drugs that inhibit osteoclast-mediated bone resorption and that have been shown to be effective for increasing bone density and decreasing risk of fracture.[2] In addition to their use in osteoporosis, bisphosphonates are used to treat Paget disease, hypercalcemia, and bone metastases.

While generally well tolerated, bisphosphonates can cause side effects such as nausea, dyspepsia, abdominal pain, muscle aches, and headaches.[3] These side effects are annoying and can affect adherence, but they do not generally cause permanent injury.

With widespread use of bisphosphonates in large populations, certain rare but serious potential side effects (such as osteonecrosis of the jaw)[4] have emerged in postmarketing surveillance. Recently, surveillance data have identified a link between certain ocular side effects and bisphosphonate use.

This article describes a case in which a patient experienced chronic conjunctivitis while using oral bisphosphonates. In order to better understand the nature of ocular side effects and to inform family physicians about their diagnosis and management, a comprehensive literature search from 1980 to December 2009 on MEDLINE and EMBASE was performed, using search terms *bisphosphonates, eye diseases, adverse effects, adverse drug reactions, chemically induced,* and *side effects*.

Case description

Mrs N. was diagnosed with osteoporosis at age 65. She was highly motivated to avoid future fractures and was prescribed 70 mg of alendronate orally once per week.

Five months later, after an upper respiratory tract infection, Mrs N. experienced acute onset of a gritty, burning sensation in both eyes. She was prescribed topical erythromycin at a walk-in clinic, but her symptoms did not improve. After months of waxing and waning symptoms, she presented to her family physician. Results of an eye examination were unremarkable. She was referred to an ophthalmologist, who prescribed topical tobramycin and dexamethasone. Her symptoms improved but then recurred after weaning this treatment. At repeat visits she had diffuse conjunctival erythema. Her ophthalmologist referred her to a colleague, who diagnosed allergic conjunctivitis. Over several months, the patient tried lubricant, vasoconstrictor and antihistamine eye drops, oral antihistamines, and elimination of potential local irritants, all without effect.

Results of a repeat bone density test showed substantial improvement, and Mrs N. chose to continue using alendronate.

Nineteen months after symptom onset, Mrs N. went on vacation and forgot to take her alendronate medication. Ten days after discontinuing the medication, her eye symptoms disappeared. On returning home, she resumed using alendronate, and symptoms recurred 2 weeks later. Once again she discontinued using alendronate, and symptoms resolved.

Mrs N. asked her pharmacist about possible eye symptoms from alendronate. The pharmacist did a brief literature search and contacted the family physician with the results.

Alerted by the pharmacist, the family physician advised Mrs N. not to take alendronate. Over the next year, she sequentially tried 35 mg of risedronate weekly, 35 mg of risedronate every 2 weeks, and etidronate. With each medication she was symptom-free for the first few weeks, then ocular symptoms recurred. After discontinuation of each bisphosphonate, eye symptoms resolved after a few days. Now Mrs N. chooses to treat her osteoporosis without bisphosphonates.

Discussion

Cases of ocular inflammation in patients taking bisphosphonates have been reported since the early 1990s.[5,6] Cases have involved both nitrogen and non-nitrogen-containing bisphosphonates (including alendronate, etidronate, risedronate, clodronate, pamidronate, and zoledronic acid).[6-18] The exact mechanism of bisphosphonate-associated ocular inflammation is not yet known.[7,11,13]

Incidence of ocular side effects cannot be determined from postmarketing adverse reaction reports.[6,12] Worldwide, numbers of reported cases are low, with

550 suspected cases listed in the World Health Organization drug monitoring database by May 2004.[9] Risk of ocular side effects might be greater with intravenous than oral bisphosphonates.[8]

Ocular side effects that have been associated with bisphosphonate treatment include conjunctivitis, uveitis, episcleritis, scleritis, and keratitis (**Table 1**).[5-10,12-20] Of those, scleritis and keratitis carry the greatest risk of long-term vision loss. Other rare conditions, such as optic neuritis and orbital or periorbital edema have occasionally been reported. Oftentimes more than 1 ocular side effect will present at the same time.[6,10,12,13] Presentation can be unilateral or bilateral.[11,12]

This case demonstrates the importance of considering drug-induced adverse effects in any differential diagnosis, but especially when a presenting complaint is not responding to common first-line therapies. Many rare and potentially serious drug-related adverse effects are not observed in randomized trials but emerge only in the postmarketing phase when large numbers of people are exposed to the drug. Family physicians are in a key position to identify these rare side effects.

This case highlights the benefits of effective collaboration between health care providers. The patient in this case presented to 5 health care providers before she recognized a possible connection between her medication and her conjunctivitis. Collaboration between pharmacist, family physician, and patient helped to effectively address her problem. Communicating with local pharmacists, as well as recognizing the value of the patient's own expertise about his or her illness, can assist primary care physicians in identifying potential drug-induced adverse effects.

Conclusion

Family physicians play a key role in identifying and managing bisphosphonate-induced ocular side effects, as they are the main care providers involved in the treatment of osteoporosis and they are frequently the first providers patients present to with eye symptoms.

Table 1. Ocular side effects associated with bisphosphonate treatment

	OCULAR CONDITION*				
CHARACTERISTICS	CONJUNCTIVITIS	EPISCLERITIS	ANTERIOR UVEITIS (IRITIS)	KERATITIS	SCLERITIS
Presenting symptoms	Conjunctival erythema, gritty irritation, tearing, vision unaffected[19,20]	Mild irritation, photophobia, erythema in episcleral vessels[19,20]	Pain, photophobia, blurred vision, orbital tenderness, injection of ciliary vessels, miosis, possible exudate in anterior chamber (hypopyon)[19,20]	Pain, erythema, decreased vision, corneal ulcerations might be visible[19,20]	Severe pain, orbital tenderness, scleral erythema[19,20]
Clues that symptoms are bisphosphonate induced	Symptoms emerge within 48-72 h (range 2 h-6 d) after initiation of parenteral bisphosphonates[5,10,13-17] and within 6-8 wk (range 1 d-3 y) after initiation of oral bisphosphonates[7,8,13,18] Symptoms do not respond to antibiotics[18] but might respond to topical or systemic corticosteroids[15,17,18] Symptoms abate soon after bisphosphonate discontinuation but might require topical or oral corticosteroids[7,13-15,18] Symptoms generally recur upon bisphosphonate rechallenge[7,9,13,17]				
Medical management†	Generally referral not required[13,17,20]	Refer depending on severity[19]	Urgent referral required[13,19,20]	Urgent referral required[13,19,20]	Urgent referral required[14,19,20]
What to do with bisphosphonate	Symptoms might improve with continuation of bisphosphonate but often bisphosphonate must be stopped[6,10,12,13,17]	Some cases reported improvement with switching to a different bisphosphonate[14]; some reported symptoms did not recur with rechallenge when prophylactic regimen was used[16]; however, in many cases the bisphosphonate must be stopped[12,13,17]			Bisphosphonate must be stopped in all cases[6,10,12,13,17]

*More than 1 ocular condition can occur simultaneously.[6,12,13]

†If any vision loss or ocular pain occurs, refer to an ophthalmologist.[6,10,17,19,20] Severe symptoms might require topical or systemic anti-inflammatories (corticosteroids, nonsteroidal anti-inflammatory drugs)[13,17,19] with or without addition of cycloplegics.[5,19]

Family doctors need to be aware of the potential for ocular side effects with this medication class. In uncomplicated cases, family physicians can manage these side effects. In more serious ocular conditions, referral to an ophthalmologist for assistance with management will be needed.

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Competing interests
None declared

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EDITOR'S KEY POINTS

- Patients with eye pain or vision loss require urgent referral to an ophthalmologist.
- Conjunctivitis might be self-limiting and might decrease in intensity over subsequent exposures, so in mild cases bisphosphonates can be continued.
- If symptoms are not severe, rechallenge with the same or a different bisphosphonate, with close monitoring. In most of the cases reviewed, rechallenge resulted in recurrence of symptoms. There is limited information on the switch to a different bisphosphonate.
- Severe symptoms and scleritis require drug discontinuation for resolution, regardless of therapy.

POINTS DE REPÈRE DU RÉDACTEUR

- Les patients qui ont mal aux yeux ou qui ont une perte de vision doivent être envoyés en consultation urgente chez un ophtalmologiste.
- La conjonctivite peut disparaître d'elle-même et peut baisser en intensité lors des expositions subséquentes; dans les cas légers, on peut donc continuer les bisphosphonates.
- Si les symptômes ne sont pas sévères, on peut reprendre le traitement avec le même bisphosphonate ou un autre et exercer une surveillance étroite. Dans la plupart des cas examinés, la reprise du traitement s'est traduite par une récurrence des symptômes. Les renseignements sont limités sur le changement pour un bisphosphonate différent.
- Les symptômes graves et la sclérite nécessitent un arrêt du médicament, quelle que soit la thérapie utilisée.

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