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Alendronate sodium and uveitis

Introduction

Alendronate sodium (Fosamax®) is a bisphosphonate that acts as a specific inhibitor of osteoclast mediated bone resorption. Bisphosphonates are synthetic analogues of pyrophosphate that bind to hydroxyapatite.
The Dutch Medicine Evaluation Board approved alendronate sodium10 mg in April 1996. This formulation is indicated for *the treatment and prevention of osteoporosis in women after menopause and the treatment and prevention of glucocorticosteroid-induced osteoporosis in man and woman with a low bone mass index (T-score,-1SD) [1].*
Five years after approval of alendronate sodium 10 mg the manufacturer launched alendronate sodium 70 mg. This formulation has the advantage of a *once-a-week* administration. The Dutch Medicine Evaluation Board approved this drug in May 2001 for *treatment of osteoporosis in women after menopause[2].*
Gastrointestinal adverse drug reactions like abdominal pain, nausea, dyspepsia, oesophageal ulcer and musculoskeletal pain and headache are reported in more than 1 percent of patients. The manufacturer claims similar drug safety profiles for both 10 and 70-mg alendronate sodium [2].

Reports on Uveitis

Until 1 January 2003 the Netherlands Pharmacovigilance Centre received a total of 5 reports concerning a suspected drug-induced uveitis. Until July 2002 we did not receive any reports concerning the association alendronate sodium and uveitis. However, in July and August 2002 we received three reports in which a relation between 70 mg alendronate once weekly and uveitis was suggested.
Case 1 A 70-year-old woman developed unilateral iridocyclitis three weeks after commencing alendronate sodium administration for osteoporosis. The symptoms resolved after treatment with ocular atropin and steroids. Concomitant drugs were nasal fluticasone and estriol vaginal cream.
Case 2 A 68-year-old female received treatment with alendronate sodium once weekly 70 mg for osteoporosis. Three months after initiation, she developed headache, angio-oedema and uveitis. The alendronate was discontinued and the patient recovered. Concomitant drugs were salbutamol and ipratropium per inhalation and calciumcarbonate.
Case 3 A 83-year-old female, with partial right eye vision (0.55) due to glaucoma, and no left eye vision due to ablatio retinae, experienced a right eye vision decrease fifteen weeks after changing the dose regimen alendronate (indication: osteoporosis) from 10 mg daily to 70mg once weekly. Her ophthalmologist noticed bilateral iridocyclitis, decreased right eye vision (0.45) and additional eye pressure increase. Alendronate was discontinued. She recovered two weeks later. Concomitant drugs were acetylsalicylic acid, fluvoxamine, atenolol, latanoprost eyedrops, colecalciferol and betaxolol eyedrops. Although the prostaglandin F_{2a} analogue latanoprost is associated with uveitis [3], the recovering two weeks after cessation of alendronate suggests an association with this drug.

Other sources of information

Literature

In the SPC of alendronate10 mg, uveitis is rarely reported in post marketing use [1]. In contrast with the SPC of alendronate 10 mg the frequency of uveitis in the SPC of alendronate 70 is based on post-marketing reports ánd clinical trials and mentioned as rare (< 1 in 1000 but > 1 in 10.000) [2].
As a pharmaceutical class, the bisphosphonates have been associated with various ocular inflammatory entities, such as scleritis, episcleritis, nonspecific conjunctivitis, and anterior uveitis [4,5].

The bisphosphonates can be divided into nitrogen containing and non nitrogen containing bisphosphonates. Most of the reported cases of uveitis followed treatment for Paget disease and hypercalcemia with intravenous pamidronate, an aminobisphosphonate [6-8]. Alendronate and risedronate, also nitrogen containing bisphosphonates are associated with uveitis to a lesser degree [7]. Salmen et al. describe a single case of acute nongranulomatous anterior uveitis associated with alendronate therapy, in an adult woman, without medical history of previous diseases, except for intercurrent osteoporosis [6]. Clodronate and etidronate, non nitrogen containing bisphosphonates, have not been associated with uveitis [5].

Databases

The WHO combination-database currently contains 10,850 possible ADRs during the use of alendronate. An association with uveitis was suggested in 12 reports. The Reporting Odds Ratio of this combination is 3.66 (95% CI 2.07-6.47).
Analysis of the Netherlands Pharmacovigilance Centre Lareb database revealed a reporting odds ratio of 212 (95% CI 42-1057) for this combination. This database contains a total of 123 possible ADRs during alendronate therapy. The minority of these possible ADRs (25) concern alendronate 70 mg. Uveitis was only reported in association with alendronate 70 mg.

Mechanism

The cause of uveitis in patients taking nitrogen containing bisphosphonates is difficult to determine. It is possible an allergic or immunological reaction caused by drug induced immune complex formation [4-7,9]. Aminobisphosfonates and related compounds are known to stimulate release of both interleukine-1 and interleukine-6, cytokines that may stimulate lymphocyte proliferation. It is possible that bisphosphonates may act as adjuvants to the immune system, causing lymphocyte proliferation and enhancement of immune complex diseases. The reason that the uvea is a target organ is unclear [4].
It has been suggested that acute inflammatory response seems unrelated to the dose of the drug, the route of administration, or the activity of Paget disease or malignancy [9]. However the fact that the Netherlands Pharmacovigilance Centre Lareb did receive three reports concerning uveitis in suspected association with 70 mg alendronic acid and did not receive any reports of uveitis in association with 10 mg alendronate sodium suggests a dose-response relationship. The strong association of uveitis with intravenous pamidronate sodium administration supports this suggestion. Perhaps are high C_{max} bloodlevels essential for penetration of these aminobiphosphonates in the uveal liquid. This hypothesis is supported by the observation that uveitis can occur in patients receiving intravitreal or intravenous cidofovir. The chemical structure of this compound bears a resemblance to the nitrogen containing bisphosphonates (Figure 1). Anterior uveitis occurs in 31 to 37% of patients with AIDS receiving intravenous cidofovir 4-5 days after institution of therapy for CMV retinitis. Intravitreal administration of this nitrogen and phosphonic acid containing potent anticytomegaloviral acyclic nucleoside analogue, can cause uveitis in 14 to 21% of the patients with AIDS [5,10].
The fact that the non nitrogen containing bisphosphonates clodronate and etidronate are not associated with uveitis has led some to speculate on the importance of nitrogen content in bisphosphonates for stimulating inflammation [7,11]. This hypothesis is supported by the observations of cidofovir induced uveitis.

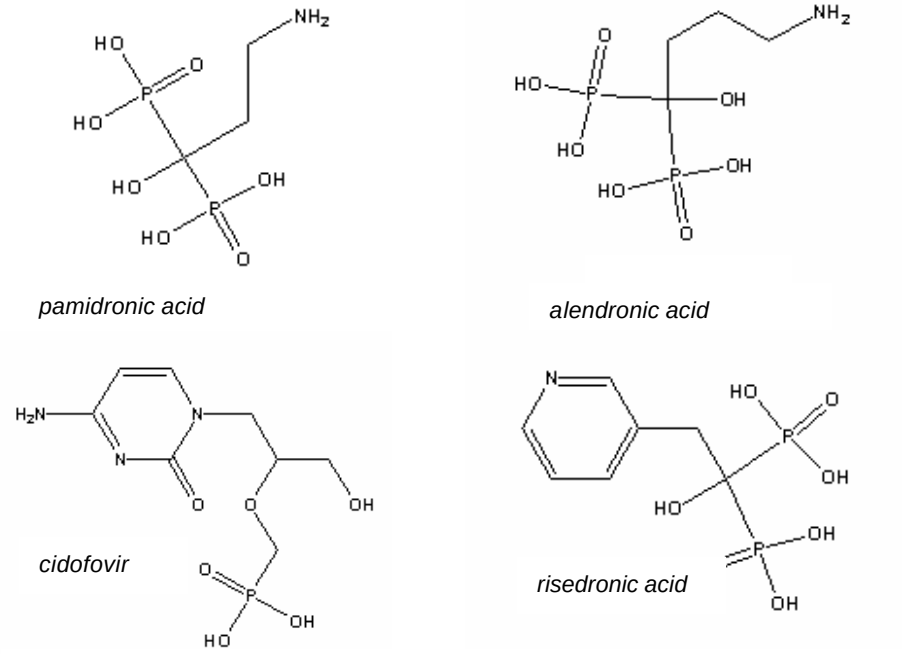

Figure 1. Chemical structures of cidofovir and the nitrogen containing pamidronic acid, alendronic acid and risedronic acid.

Conclusion

The fact that the Netherlands Pharmacovigilance Centre did receive three reports concerning uveitis in suspected association with 70 mg alendronic acid and did not receive any reports of uveitis in association with 10 mg alendronate sodium suggests an increased incidence of alendronate sodium induced uveitis due to the availability of the 70 mg tablets. This observation suggests a dose-response relation.

References

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