

Gülcan ÖZTÜRK¹
Ece AYDOĞ²
Duygu GELER KÜLCÜ³



CASE REPORT

CONJUNCTIVITIS AS A RARE SIDE-EFFECT OF RISEDRONATE: A CASE REPORT

ABSTRACT

Osteoporosis is common metabolic bone disease in older people. Bisphosphonates is usually used in the management of osteoporosis. However, a small number of patients have been recognized to develop ocular inflammation due to administration of bisphosphonates. We report the case of risedronate-induced conjunctivitis in a 68-year-old woman. This was successfully treated with stopping risedronate. Applying Naranjo's adverse drug reaction probability scale, a causality assessment was made which categorized this reaction as probable with a score of 7. This case report reviews the literature on the ocular effects of risedronate and discusses a possible mechanism for the association. Although ocular adverse effects of bisphosphonates are rare, it may effect eyesight. Physical Medicine and Rehabilitation clinicians should be aware of ocular side-effects in older patients because a delay in diagnosis may result in serious adverse outcomes.

Key Words: Aged; Osteoporosis; Risedronate; Conjunctivitis.



OLGU SUNUMU

RİSEDRONATA BAĞLI GELİŞEN NADİR BİR YAN ETKİ; KONJUNKTİVİT: OLGU SUNUMU

Öz

Osteoporoz yaşlılarda sık karşımıza çıkan metabolik bir kemik hastalığıdır. Osteoporoz tedavisinde genellikle bifosfanatlar kullanılır. Bununla birlikte, bifosfanat grubu ilaçların az sayıda hastada gözde inflamasyon bulgularına neden olduğu bildirilmiştir. Bu çalışmada risedronat kullanımının neden olduğu konjunktivit tablosuyla gelen ve risedronatın kesilmesi konjunktivit semptomlarının gerilediği 68 yaşında bayan hastayı sunduk. Naranjo'nun ilaç yan etki olasılığı ölçeğine göre 7 puan alan hastamız, kuvvetle muhtemel kategorisine uymakta idi. Bu olgu sunumu aracılığıyla bifosfanat grubu ilaçların göz üzerine olan yan etkilerini hatırlatmayı ve olası etki mekanizmasını tartışmayı amaçladık. Bifosfanatların göz üzerine olan yan etkileri nadir olmasına rağmen, görme bozukluklarına neden olabilir. Fiziksel tıp ve rehabilitasyon hekimleri yaşlı hasta popülasyonunda bu yan etkiler açısından dikkatli olmalıdır; gecikmiş tanı görme kayıplarına neden olabilir.

Anahtar Sözcükler: Yaşlı; Osteoporoz; Risedronat; Konjunktivit.

Correspondance

Gülcan ÖZTÜRK
Gebze Fatih State Hospital, Physical and Rehabilitation
Clinic, KOCAELİ

Phone: 0262 644 14 60
e-mail: drgul_can@hotmail.com

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¹ Gebze Fatih State Hospital, Physical and Rehabilitation
Clinic, KOCAELİ

² Yeditepe University, Physical and Rehabilitation Clinic,
İSTANBUL

³ Haydarpaşa Numune Training and Research Hospital,
Physical and Rehabilitation Clinic, İSTANBUL



INTRODUCTION

Bisphosphonates (BPs) are frequently used for the prevention and/or treatment of osteoporosis (1). They are divided into two groups: nitrogen and non-nitrogen. The nitrogen group includes pamidronate, alendronate, risedronate, ibandronate, and zoledronic acid, while the non-nitrogen group includes etidronate and clodronate (2). Risedronate, a nitrogen BP, modulates bone metabolism at the cellular level by inhibiting farnesyl diphosphate synthetase and inducing osteoclast apoptosis (3).

Bisphosphonates are well tolerated in general; however, they can occasionally cause side-effects. Most common side-effects include nausea, dyspepsia, abdominal pain, and myalgia (1). Ocular side-effects are rare, but can be serious. Occurrences of conjunctivitis, uveitis, scleritis, episcleritis, optic or retrobulbar neuritis, cranial nerve palsy, and ptosis have been previously reported (4). Ocular side-effects have been associated with the use of both nitrogen (i.e., pamidronate, alendronate, zoledronate, and risedronate) and non-nitrogen groups (i.e., etidronate) (2). For risedronate, scleritis, episcleritis, and ocular myasthenia gravis each have been reported only once, and three cases of conjunctivitis associated with its use have been described (5-7).

Here we report the case of risedronate-induced conjunctivitis in a 68-year-old woman. To the best of our knowledge, this is the fourth case report on risedronate-induced conjunctivitis treated with fusidic acid and discontinuation of risedronate.

CASE

A 68-year-old woman with back pain was admitted to our Physical Medicine and Rehabilitation (PMR) outpatient clinic. Her pain began six months prior. Although she did not report morning stiffness or pain at night, she explained that her pain increased with exercise and decreased with rest. She visited a different PMR clinic six months prior for a rehabilitation program; however, her pain continued. Although she had been diagnosed with osteoporosis in 2006 based on her bone mineral density findings [T scores were -2.6 and -2.5 standard deviations (SDs) for the lumbar region (L1-L4) and femoral neck, respectively], she was not under any medication for osteoporosis on admission. On physical examination, it was revealed that the spinal processes in the lower thoracic and lumbar vertebrae were painless to palpation. The lumbar range of motion was painful in all directions. Plain radiog-

raphs of the dorsal (anterior-posterior and lateral) region revealed height loss in the dorsal vertebrae and degenerative changes. Her bone mineral density examination revealed T scores of -3.5 and -3.4 SDs for the lumbar region (L1-L4) and femoral neck, respectively. Laboratory investigation revealed normal values for blood cell counts and normal serum levels of calcium, phosphorus, parathyroid hormones, alkaline phosphatase, and 25-OH-vitamin D3.

Treatment with risedronate (150 mg/month), calcium (1 g/day), and vitamin D (880 IU/day) supplementation was initiated. Six hours after the first oral administration of risedronate, she developed right conjunctival hyperemia, photophobia, and pain (Figure 1). Her vision was not affected, and there was no mucopurulent secretion from the eyes. An ophthalmologist was consulted, and she was diagnosed with conjunctivitis as a risedronate-induced side-effect. Applying Naranjo's adverse drug reaction probability scale, a causality assessment was made, which categorized this reaction as probable with a score of 7. Therefore, risedronate administration was stopped and topical fusidic acid administration was initiated by the ophthalmologist. Because the conjunctivitis was considered to be a risedronate-induced side-effect, the ophthalmologist emphasized that fusidic acid should be used for prophylaxis of future bacterial infections. Two weeks after discontinuing risedronate and using fusidic acid, her eye symptoms disappeared.

DISCUSSION

Bisphosphonates have been widely used to treat various diseases, including osteoporosis, bone metastasis, Paget's disease, hypercalcemia, and other conditions associated with bone resorption (1,2). In addition, an anti-tumor effect from



Figure 1— Conjunctival hyperemia on the right eye.



these medications has been observed in patients with cancer without metastasis in recent years (9). Based on these findings, it is probable that BPs usage will increase in the future as well. The most common side-effects of BPs include nausea, dyspepsia, abdominal pain, myalgia (2). Cases of ocular side-effects in individuals taking BPs have been reported since 1993; the first report for risedronate was published in 2002 by Vinas *et al.* (9). However, ocular side effects with this class of medication are uncommon with an estimated incidence around 0.05% (5,10). The cases included occurrences of conjunctivitis, uveitis, scleritis, optic or retrobulbar neuritis, and cranial nerve palsy (2,11).

The exact mechanisms underlying the ocular side-effects attributable to BPs remain unclear.

Ocular inflammation may be caused by the localized manifestations of a systemic adverse reaction to a drug. BP-induced ocular inflammation has also been associated with systemic acute-phase reactions, such as fever and influenza-like symptoms. BPs are associated with human T-cells that are key players in the interface between innate and adaptive immunity (12). BPs stimulate the production of a distinct subgroup of T-cells that constrain bone resorption. As a synthetic analogue of inorganic pyrophosphates, these drugs share several homologies with non-peptide gamma-delta T-cell ligands that activate the gamma-delta T-cell antigen receptors; this activation releases cytokines and inflammatory mediators (7,12,13). Therefore, BPs induce immunologic or toxic reactions, resulting in the release of inflammatory cytokines such as tumor necrosis factor- α , interleukin-6, and other cytokines. Although, in recent literature, ocular inflammation has been postulated as a localized manifestation of a systemic adverse reaction to the drug (1), the reason why the eye has been a target organ remains unknown (2,6,13,14).

In recent studies, there have been no underlying diseases associated with BP-induced ocular inflammation; therefore, the predisposing factors for this inflammation have not yet been elucidated (10). Some authors have indicated that ocular inflammation can also be a sign of systemic rheumatic disease, but most of these affected patients had no underlying conditions (10). In inflammatory ocular diseases that are associated with rheumatic diseases such as systemic lupus erythematosus and rheumatoid arthritis, IL-6, an inflammatory cytokine, has been responsible for causing ocular inflammatory reactions similar to those with BPs. IL-8 also contributes to ocular and orbital inflammation by promoting neutrophil and T-cell recruitment to the eye (15). It is unclear whether the ocular side-effects attributable to BPs are a direct side-effect or an

effect associated with underlying disease, particularly rheumatic disease (2). Furthermore, although patients who have rheumatic disease may require treatment with steroids, BPs may be used to prevent corticosteroid-induced osteoporosis or rheumatic disease-induced osteoporosis. For example, Pazianas *et al.* showed increased ocular side-effects related to BPs in rheumatic disease; this study revealed that one in five patients treated with alendronate had known rheumatic disease and one in 20 had been treated with topical eye steroids in the past year (2). Thus, further studies are needed to reveal the exact mechanism for inflammation in rheumatic diseases and also that with BP usage. In the present case, there were no positive rheumatic assessment findings.

Risedronate-related ocular side-effects have infrequently been presented in the literature and based on our literature search, we found that ocular side effects can have a relatively rapid onset (within a few hours of administration) or can appear as long as six years after the administration of the drug (2,17). Three weeks has been reported as the average time to the onset (2). Barrera *et al.* published the results of an observational study of 13,164 risedronate-treated patients in England and detected 19 adverse events, including three cases of conjunctivitis and one case of episcleritis. They described conjunctivitis as a side-effect of risedronate on days 14, 29, and 100 of administration (3). Hemmati *et al.* described risedronate-associated scleritis (7). In this case, the symptoms started on the day risedronate was started. After reviewing the patient's detailed medical history, the authors found that there were similar eye symptoms two years prior while using a smaller dosage of risedronate. Similar to the Hemmati *et al.* case, Geneva *et al.* presented two cases of conjunctival squamous metaplasia that were related to risedronate sodium. The detailed medical histories for these patients revealed previous use of risedronate. However, unlike the previous cases, one patient had been treated with risedronate for six years. The authors explained that the possible mechanism was ocular inflammation, similar to that in BP-induced conjunctivitis (17). Table 1 summarizes the ocular findings of the reported cases from the literature that were associated with risedronate therapy. It is important to consider BP-induced ocular side effects in the medical history. In the current report, we describe the occurrence of risedronate-induced conjunctivitis in a 68-year-old woman, which occurred 6 h after the first oral administration of risedronate. Applying Naranjo's adverse drug reaction probability scale, a causality assessment was made, which categorized this reaction as probable with a score of 7 (18). BP-induced conjunctivitis or episcleritis usually has a good prognosis, and the symptoms generally resolve without



specific treatment. Non-steroidal anti-inflammatory eye drops often can resolve the symptoms as well (10). To the best of our knowledge, this is the fourth case of risedronate-related conjunctivitis. In this case, discontinuing risedronate treatment and initiating prophylactic treatment with fusidic acid to prevent future infections resulted in an improvement in two weeks.

In conclusion, osteoporosis is common in older people. BPs are prescribed for the prevention and treatment of osteoporosis. Although rare, it is important to consider BP-induced ocular adverse effects. With the increasing use of BPs, PMR clinicians and rheumatologists should be aware of the possibility for rare ocular side-effects of BPs and should obtain a detailed drug history. A delay in diagnosis can allow the development of contralateral eye involvement or recurrent and chronic inflammation that may result in adverse visual outcomes.

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