

Bisphosphonates and blurred vision

Introduction

Bisphosphonates are used in *primary and secondary prevention in the treatment of postmenopausal osteoporosis and in glucocorticosteroids induced osteoporosis* because of their effect on the bone resorption. Bisphosphonates have a direct inhibiting effect on the osteoclasts through which bone mass increases [1]. Some of the bisphosphonates, like pamidronate and zoledronate, are also used *in patients with advanced malignancies involving the bone and for the treatment of tumour-induced hypercalcaemia*.

Bisphosphonates currently available on the Dutch market are alendronate (Fosamax[®]), clodronate (Bonefos[®]), etidronate (Didronel[®]), ibandronate (Bonviva[®]), pamidronate (Pamipro[®]), risedronate (Actonel[®]) and zoledronate (Zometa[®]) [1-7]. Overall, bisphosphonates are available as oral administration. Ibandronate is also available as intravenous infusion. Zoledronate and pamidronate are only available as intravenous infusion. Alendronate is the most widely prescribed bisphosphonate in the Netherlands with 139,810 users in 2011 (Table 5).

Blurred vision usually refers to decreased visual acuity of gradual onset. The most common causes of blurred vision include: refractive errors, age-related macular degeneration, cataracts, and diabetic retinopathy [8].

Reports

Until March 22nd 2013, the Netherlands Pharmacovigilance Centre Lareb received 20 reports concerning blurred vision associated with the use of bisphosphonates, see Table 1a-c. These reports concern the use of alendronate (13), risedronate (6) and ibandronate (1). All reports were made by healthcare professionals, except for report K and L which were made by a consumer.

The mean age of all patients is 72 years with a standard deviation of 10 years. The outcome of the reaction was reported in 10 cases. Four patients (D,H,L,S) recovered after withdrawal of the bisphosphonate. One patient (S) also had a positive rechallenge. Two patients were recovering, one after dose reduction (K) and one after withdrawal (N) of the bisphosphonate. Three patients did not recover after drug withdrawal (C,E,O).

Table 1a. Reports of blurred vision associated with the use alendronate

Patient, Number, Sex, Age, Source	Drug, daily dose Indication for use	Concomitant Medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
A 18042 F, 61-70 General Practitioner	alendronate tablet 10mg once a day	simvastatin amlodipine atenolol	vision blurred, nausea	3 days discontinued not reported
B 26859 F, 71 or older General Practitioner	alendronate tablet 10mg once a day osteoporosis	budesonide, prednisolone betahistine aluminium oxide	vision blurred, taste perversion, abdominal discomfort, dyspnoea	7 weeks discontinued not reported
C 33903 F, 71 or older Pharmacist	alendronate tablet 70mg once a week osteoporosis	diazepam, paracetamol, amlodipine, homeopathic tablets, hypromellose eye drops, rabeprazole, irbesartan, chlorotalidone	vision blurred	1 hour discontinued not recovered

D 47059 F, 61-70 General Practitioner	alendronate tablet 10mg once a day osteoporosis	paracetamol	diarrhoea, vision blurred, concentration impaired, nausea	9 days discontinued recovered
E 53830 F, 61-70 Pharmacist	alendronate tablet 70mg once a week osteoporosis	fluticason nasal spray, calcium, plantago ovata	vision blurred, therapeutic response unexpected with drug substitution, dizziness, vomiting	2 days discontinued not recovered
F 53977 F, 51-60 Pharmacist	alendronate tablet 70mg once a week		arthralgia, vision blurred, eye discharge	10 weeks no change unknown
G 56214 F, 71 or older Specialist doctor	alendronate tablet 70mg once a week osteoporosis	calcium	vision blurred	2 years discontinued unknown
H 59101 F, - Pharmacist	alendronate tablet 70mg		arthralgia, vision blurred	2 weeks discontinued recovered
I 61814 F, 61-70 Pharmacist	alendronate tablet 10mg once a day		headache, vision blurred, musculoskeletal pain, dyspepsia	1 week discontinued unknown
J 62669 F, 71 or older General Practitioner	alendronate tablet 70mg once a week osteoporosis	calcium/ colecalfiferol	vision blurred	not reported discontinued unknown
K 66215 F, 61-70 Consumer	alendronate tablet 70 mg once a week estriol vaginal cream 1mg/g twice a week osteoporosis, vaginal dryness	zopiclone, glucosamine	headache, arthralgia, vision blurred, bone pain, myalgia, palpitations	3 months dose reduction not yet recovered
L 133984 F, 41-50 Consumer	alendronate tablet 10mg once a day osteoporosis	betahistine	headache, arthralgia, blurred vision, chest pain, malaise, spasms, dizziness, fatigue, pyrosis, breathing difficult, upper abdominal pain, alopecia	7 months discontinued recovered
M 144505 F, 71 or older Pharmacist	alendronate 10 mg once a day, alendronate tablet 70 mg once a week osteoporosis	calcium/ colecalfiferol, omeprazole, acetylsalicylic acid , ezetimibe , pravastatin	joint swelling, exanthema, facial pain, injury to teeth, blurry vision	3 years, discontinued unknown

Table 1b. Reports of blurred vision associated with the use risedronate

Patient, Number, Sex, Age, Source	Drug, daily dose Indication for use	Concomitant Medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
N 32095 F, 51-60	risedronate tablet 30mg once a day	esomeprazole, estradiole,	arthralgia, vision blurred,	19 days discontinued

General Practitioner		zolpidem	chest ache, vertigo, dyspnoea	not yet recovered
O 51824 F, 71 or older Pharmacist	risedronate tablet 35mg once a week, calcium carbonate tablet 500mg six times a week	insulin, rosuvastatin, furosemide, folic acid, acetylsalicylic acid, levomenthol/coal tear shampoo, paracetamol/ codeine , insulin	vision blurred	14 days discontinued not recovered
P 52178 F, 71 or older Pharmacist	risedronate tablet 35mg once a week	pantoprazole	vision decreased, vision blurred	8 month unknown unknown
Q 65237 F, 71 or older Pharmacist	risedronate tablet 5mg once a day osteomalacia	esomeprazole, epoetin Beta, ipratropium/ salbutamol	diarrhoea, vision blurred, dizziness	6 days no change unknown
R 117782 F, 71 or older Pharmacist	risedronate tablet 35mg once a week, furosemide tablet 40mg twice a day	calcium/ colecalciferol, paracetamol tablet, hydrochlorothiazide/ irbersartan	blurred vision	not reported no change not recovered
S 136878 M, 71 or older Pharmacist	risedronate tablet 35mg once a week osteoporosis prophylaxis	omeprazole, prednisolone, nitroglycerine oromucosal spray , isosorbide nitrate, temazepam, calcium/ colecalciferol, hydrochlorothiazide , quinapril	blurred vision	hour no change recovered

Table 1c. Reports of blurred vision associated with the use ibandronate

Patient, Number, Sex, Age, Source	Drug, daily dose Indication for use	Concomitant Medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
T 110360 F, 51-60 Pharmacist	ibandronate tablet 150mg once a month	letrozole, calcium/ colecalciferol	headache, vision blurred, gait disturbance, hyperhidrosis, flushing	2 hours discontinued unknown

Patient C, J and L consulted an ophthalmologist but no abnormalities were found. Patient D experienced the same reactions after administration of risedronate once a week. In patient G an uveitis was ruled out by a specialist doctor. Patient O has diabetes mellitus but the reporter stated that it is very clear that the blurred vision occurred 14 days after administration of risedronate. Patient S reported that the blurred vision occurred the first and second day after administration of risedronate. The patient had noticed this since five weeks. Once he forgot to take the risedronate tablets and he noticed that his sight was normal. This patient also has temporal arteritis but the reporter reports that this condition has a very specific image of complaints and a relation with temporal arteritis is unlikely. Patient T experienced the reactions four times within a period of 11 months. Each time the reactions occurred two hours after administration of ibandronate. The patient switched to alendronate administrated once a week and the same reactions occurred but with a latency time of 4-6 hours.

Other sources of information

SmPC

Blurred vision is not described in the SmPCs of the various bisphosphonates [1-7]. Blurred vision is reported as possible adverse drug reaction in the SmPC of alendronate in combination with colecalciferol [9]. It is described that this drug has no or negligible direct influence on the ability to drive and use machines. Adverse reactions (for example blurred vision, dizziness and severe bone muscle or joint pain) that have been reported may affect some patients' ability to drive or operate machines.

Literature

In literature, little is found about blurred vision associated with the use of bisphosphonates. Bisphosphonates are associated with ocular adverse drug reactions that are mainly inflammatory, i.e. conjunctivitis, uveitis and episcleritis [10]. Blurred vision can be associated with an inflammatory adverse drug reaction. Two studies were found where the use of bisphosphonates was associated with blurred vision [11,12]. Izumi et al. [12] explored whether risedronate recovered decreases in bone mineral density of the lumbar spine caused by androgen deprivation therapy through 24 months. As adverse effects transient blurred vision, malaise and vertigo were observed in 1 patient each among the 46 patients treated with risedronate within 28 days after the first administration. The symptoms in this patient improved immediately after risedronate was discontinued. Fraunfelder et al. [11] classified ocular side effects associated with pamidronate using the World Health Organization Causality Assessment Guide. In this study more than one possible adverse ocular event may have occurred in each patient. The most commonly reported adverse drug effect due to pamidronate was nonspecific conjunctivitis. This was usually manifested as bilateral conjunctival hyperemia, with or without epiphora, mucus discharge, or blurred vision. They also found blurred vision as separate reaction to be a 'certain' adverse drug effect of pamidronate; plausible time relationship to drug administration and blurred vision cannot be explained by concurrent disease or other drugs or chemicals.

Database

The Lareb database was searched for all bisphosphonates with ATC-code M05BA in association with the MedDRA Preferred Term (PT) vision blurred. On March 22th, 2013 the Lareb database contained 20 reports for this association, see Table 3. Since there is only one reports of blurred vision associated with ibandronate, the reporting odds ratio (ROR) could not be calculated for this association. The reporting odds ratio (ROR) was disproportional for blurred vision associated with alendronate (ROR=3.3, 95% CI: 1.9-5.7) and risedronate (ROR= 4.2, 95% CI: 1.9-9.5). The ROR for blurred vision was not disproportional reported for the total group of bisphosphonates (ROR = 1.3, 95% CI: 0.9-2.1).

The WHO database of the Uppsala Monitoring Centre contained 617 reports of blurred vision associated with the use of bisphosphonates, see Table 4. The ROR was not disproportional for the total group of bisphosphonates but was for alendronate (ROR = 1.37, 95% CI: 1.20-1.56), pamidronate (ROR= 2.56, 95% CI: 3.16-3.91), and zoledronate (ROR = 1.54, 95% CI: 1.75-1.99).

The Eudravigilance database of the EMA contained 616 reports of blurred vision for the bisphosphonates. In this database the association is proportionally present for the entire group of bisphosphonates. See Table 5.

Table 3. Reports of blurred vision associated with the use of bisphosphonates in the database of the Netherlands Pharmacovigilance Centre Lareb

Drug	Number of reports	ROR (95% CI)
Alendronate	13	3.3 (1.9-5.7)
Risedronate	6	4.2 (1.9-9.5)
Ibandronate	1	N.A.

Bisphosphonates (total)	20	1.3 (0.9-2.1)
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Table 4. Reports of blurred vision associated with the use of bisphosphonates in the database of the WHO

Drug	Number of reports	ROR (95% CI)
Alendronate	226	1.4 (1.2-1.6)
Clodronate	2	N.A.
Etidronate	2	N.A.
Ibandronate	67	0.8 (1.0-1.3)
Pamidronate	89	3.2 (2.6-4.0)
Risedronate	77	1.8 (1.5-2.0)
Zoledronate	243	1.7 (1.5-2.0)
Bisphosphonates (total)	706	0.6 (0.6-0.7)

Table 5. Reports of blurred vision associated with the use of bisphosphonates in the Eudravigilance database

Drug	Number of reports	ROR (95% CI)
Alendronate	160	1.4 (1.2-1.7)
Clodronate	1	N.A.
Etidronate	3	2.0 (0.7-6.2)
Ibandronate	36	1.1 (0.8-1.5)
Pamidronate	115	4.0 (3.3-4.8)
Risedronate	34	1.5 (1.1-2.1)
Zoledronate	309	1.9 (1.7-2.1)
Bisphosphonates (total)	657	1.8 (1.7-2.0)

Prescription data

The number of users for the various bisphosphonates in the Netherlands is given in Table 6.

Table 6. Number of bisphosphonate users in the Netherlands between 2007 and 2011 [13]

	2007	2008	2009	2010	2011
Alendronate	139,810	141,100	141,610	144,060	144,580
Clodronate	3,082	2,935	2,712	2,406	2,133
Etidronate**	9,295	7,115	5,445	4,346	3,285
Ibandronate	8,481	10,762	11,434	11,804	11,868
Pamidronate	NA	NA	NA	NA	NA
Risedronate	61,755	66,142	69,883	70,786	67,919
Zoledronate	452	605	1,367	2,447	3,216

** only numbers available for etidronate in combination with calcium (Didrokit®)

NA = Not available

Mechanism

The mechanism by which bisphosphonates may cause blurred vision, in cases where there are no signs of an underlying eye inflammation, is unknown. In literature no information on a possible mechanism could be found.

Discussion and conclusion

Lareb received 20 reports of blurred vision associated with the use of bisphosphonates; alendronate (13), risedronate (6) and ibandronate (1). The ROR of the Lareb database was disproportional for alendronate and risedronate. In the database of the WHO blurred vision was reported for all bisphosphonates with a total of 617 reports. The ROR was disproportional for alendronate, pamidronate, and zoledronate. The ROR for the bisphosphonates as a group was also disproportional in the Eudravigilance database. In some cases contaminant medication may be confounding the association. For example proton pump inhibitors, letrozole or hydrochlorothiazide are associated with visual disturbances [13-15]. However, the detailed description of the occurrence of the blurred vision and the positive dechallenge in four cases are strong indications for an association with the use of bisphosphonates.

Bisphosphonates are known to be associated with inflammatory ocular adverse effects, i.e. conjunctivitis, uveitis and episcleritis [10]. Blurred vision can be a symptom of such reactions. In literature two studies were found in which blurred vision was observed in association with bisphosphonates [11,12]. In the study of Fraunfelder et al. [11] was noted that more than one possible adverse ocular event may have occurred in each patient. It cannot be excluded that the patients in this study who experienced blurred vision also had an inflammatory ocular adverse reaction.

The cases reported to Lareb contain little information on test results. In the cases described here, except for patient F, no inflammatory eye reactions were reported or could be taken into consideration on the basis of the reported information. A few patients even saw a specialist doctor and no abnormalities of the eyes were found. This indicated that there might be another underlying mechanism for the blurred vision.

Blurred vision is a new signal associated with the use of bisphosphonates. Further investigation of blurred vision in association with bisphosphonates of the marketing authorization holders is advisable.

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References

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This signal has been raised on July 2013. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB www.cbgmeb.nl/cbg/en/default.htm or the responsible marketing authorization holder(s).