1.1. Bisphosphonates and stomatitis

Introduction

Bisphosphonates are used in primary and secondary prevention in the treatment of postmenopausal osteoporosis because of their effect on the bone resorption and are also indicated as prophylaxis in glucocorticosteroid induced osteoporosis. 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 [2,3]. Bisphosphonates currently on the Dutch market are etidronate (Didronel®), clodronate (Bonefos®), pamidronate (Pamipro®), alendronate (Fosamax®), tiludronate (Skelid®), ibandronate (Bonviva®), risedronate (Actonel®), zoledronate (Zometa®) and the combination preparations etidronic acid/ calciumcarbonate (Didrokit®), risedronate/ calciumcarbonate (Actokit®) and alendronate/cholecalciferol (Fosavance®) [1-11]. Alendronate is the most widely prescribed bisphosphonate in the Netherlands with 138,250 users in 2007 (Table 2) [12].
Stomatitis is defined as an inflammation of the mucosa of any of the structures in the mouth, which may involve the cheeks, gums, tongue, lips, and roof or floor of the mouth [13]. Stomatitis is not mentioned in the SmPC of the bisphosphonates on the Dutch market, except for the SmPC of zoledrate [2]. Glossitis, which can be part of stomatitis, is mentioned in the SmPCs of risedronate, risedronate/calcium and etidronate/calcium.
This report describes the association between bisphosphonates and stomatitis.

Reports

Until January 26, 2009 the Netherlands Pharmacovigilance Centre Lareb received 12 reports concerning stomatitis associated with the use of bisphosphonates (Table 1). In these reports, stomatitis, mouth irritation, aphthous stomatitis and ulcerative stomatitis were mentioned.
In eight reports, alendronate was used as suspect medication. Three reports concerned the use of etidronate with calciumcarbonate and one report concerned the use of risedronate. All reports were made by health professionals, except for patient E (consumer) and patient H (Marketing Authorisation Holder). In most reports, latency time was less than two weeks.
The outcome of the reaction was reported in 11 cases; 10 patients recovered or are recovering at the time of reporting. One patient did not recover after drugwithdrawal. Six patients recovered (A, G, K and L) or were recovering (H, I) after discontinuation of the drug at the time of reporting. Two patients (D, E) recovered after dose reduction from alendronate 70 mg once weekly to 10 mg once daily. Another two patients (C, F) recovered after switching to risedronate.
In seven out of 12 reports, calcium carbonate was used as combination preparation with the suspected drug or was used as concomitant medication. Two reporters explicitly mentioned that the symptoms started after the intake of calcium tablets (patients K and L).
Patient H chewed on the tablets before swallowing them. In all other reports, is it unknown how patients took their tablets.

Table 1. Reports of stomatitis associated with the use of bisphosphonates.

Patient, Number, Sex, Age	Drug, daily dose Indication for use	Concomitant Medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome

A 18868 F, 52	alendronate 10mg 1dd osteoporosis	clonazepam oxazepam	taste alteration restlessness mouth irritation	25 day discontinued recovered rechallenge pos.
B 35290 F, age not reported	alendronate 70mg weekly osteoporosis	triamterenum/epitizide paracetamol/codeine calcium/ cholecalciferol	headache stomatitis	not reported dose reduction to 10 mg recovered
C 41608 F, 62	alendronate 70mg weekly	folic acid misoprostol etanercept rabeprazole methotrexate indomethacin etalpha alfacalcidol calcium carbonate	mouth irritation mouth dry	1 hour after intake of every tablet, duration 2 days Discontinued, switch to risedronate. recovered
D 37225 F, age not reported	alendronate 70mg weekly osteoporosis	furosemide fenoterol/ipratropium	stomatitis	not reported dose reduction to 10 mg recovered
E 47515 F, 58	alendronate 70mg weekly osteoporosis	none reported	taste alteration stomatitis oesophagitis	2 week discontinued not recovered after 4 months
F 50949 F, 67	alendronate 70mg weekly postmenopausal osteoporosis	calcium/ cholecalciferol	stomatitis	unknown days, duration 3 days discontinued, switch to risedronate. recovered
G 31336 F, 74	alendronate, dose not specified osteoporosis	acetylsalicylic acid	ulcerative stomatitis	12 day discontinued recovered after 1 month
H 32100 F, 58	alendronate 10mg 1dd*	calcium	oral ulceration, ulcerative oesophagitis	9 days discontinued recovering
I 70551 F, 77	risedronate 35mg weekly osteoporosis	none reported	stomatitis	4 week discontinued recovering
J 17319 F, 69	etidronate/ calciumcarbonate 400/500 mg	salbutamol levothyroxin	aphthous stomatitis pruritus	a few days no change unknown
K 32047 F, 72	etidronate/ calciumcarbonate 400/500 mg prophylaxis osteoporosis	insulin simvastatin carbasalate calcium amlodipine furosemide prednisone	stomatitis	10 day discontinued recovered
L 13841 F, 68	etidronate/ calciumcarbonate 400/500 mg osteoporosis	temazepam	stomatitis	14 day not reported discontinued recovered

* The reporting general practitioner felt the oral ulceration and ulcerative oesophagitis were due to alendronate, but the patients' specialist disagreed with this opinion.

Other sources of information

SmPC

The SmPC of zoledronate, which is given by infusion, mentions stomatitis as a well known Adverse Drug Reaction (ADR) [2]. This supports a mechanism that is not related to direct contact between the oral mucosa and zoledronate.

Literature

In literature, three case reports about bisphosphonate-associated stomatitis were found. No literature was found about stomatitis in relation with the use of calcium carbonate. In all case reports about bisphosphonate-associated stomatitis, the patients held the drug in their mouth before swallowing them [14-16]. Rubegni *et al*. describe a 68-year-old woman with erosive mucositis of the hard palate while using alendronate. Previous treatment with several systemic and topical drugs was unsuccessful. After proper instructions for intake of alendronate, the contact stomatitis improved in two weeks. After one year, the oral ulceration had not recurred [14].

Demerjian *et al*. describe a patient with severe oral pain four days after start of alendronate. The patient had sucked on the alendronate tablets. After drugwithdrawal and regular mouth wash, the patient recovered after seven days. The authors mention a toxic effect leading to direct mucosal injury [16].

Because of these adverse effects on the mucosa, the authors of two case reports advise that several preventive measures must be taken while taking the drug [15,16].

Gonzalez-Moles et al. [15] describe two cases with ulcerations during the use of alendronate. The first case concerns a patient who kept the drug on her tongue for a few seconds whilst she went for a glass of water; the second patient held alendronate in her mouth until it completely dissolved. Both patients used upper protheses that they did not remove when taking alendronate. They developed extensive ulcers on the palate and one of them also had ulcers of the tongue and lower lip. It is remarkable that both patients had long latency times (five months and one year) before symptoms occurred and both patients had the same type of palatal ulcers. The lesions disappeared slowly after withdrawal of the drug.

Databases

Until January 2009, the Lareb database contained 12 reports of stomatitis with the use of bisphosphonates, with a reporting odds ratio which is not disproportional (ROR 1.3, 95% CI 0.7-2.3).

The majority of the reports concerned the use of alendronate. The reporting odds ratio of alendronate in relation to stomatitis was disproportionally present in the Lareb database (ROR 2.7, 95% CI 1.3-5.4).

Until January 2009, the WHO Collaborating Centre database contained 874 reports of aphtous, necrotising, ulcerative or non specified stomatitis with the use of alendronate, etidronate, clonronate, ibandronate, pamidronate, risedronate and zoledronate. These reports were disproportionally represented (ROR 7.2, 95% CI 6.7-7.8).

On February 13 2009 the Eudravigilance database, that contains reports of mainly serious ADRs, contained 136 reports of stomatitis associated with bisphosphonates. All but seven reports concerned serious ADRs, with age ranged from 36 to 99 years. Twenty-two males were involved, 95 females, and sex not specified in seven cases. In seven cases oral aphtae were part of a reaction leading to death. In 30 cases reaction led to disability, in 47 to hospitalization, and in three to another life threatening reaction. It is unlikely that the seriousness of the reported ADRs was related to stomatitis.

Prescription data

Table 2. Total numer of users of bisphosphonates in 2007 (Source: GIP databank [12]).

Drug	Users in 2007
etidronate (Didronel®)	0
clodronate (Bonefos®)	3,053
pamidronate (Pamipro®)	0
alendronate (Fosamax®)	138,250
tiludronate (Skelid®),	20
ibandronate (Bonviva®)	8,379
risedronate (Actonel®)	61,088
zoledronate (Zometa®)	447
etidronic acid/ calciumcarbonate (Didrokit®)	9,195
risedronate/ calciumcarbonate (Actokit®)	12,267
alendronate/cholecalciferol (Fosavance®)	17,697

Mechanism

It is likely that mouth ulcerations are the result of a direct irritating effect on the mucosa of the mouth [14-16]. On the other hand, Gonzalez-Moles *et al.* propose a more immunity related reaction, because of the long latency time. The palatal ulcers of the two cases were quite similar and the same appearance as oral ulcers that arise from immunity disorder-related diseases [15].

Discussion

Lareb received 12 reports of stomatitis with the use of a bisphosphonate. In the majority of the reports, stomatitis was associated with the use of alendronate. It is not clear how patients took their tablets. The SmPCs of bisphosphonates mention instructions for proper use to reduce the irritating effect on the mucous. However, ten patients recovered or were recovering after drug withdrawal or dose reduction, suggesting a causal relationship.

In seven cases, calcium carbonate was also used. Two reporters mentioned stomatitis beginning after the start of calcium.In these two cases, calcium was started later than the bisphosphonate. However, the literature revealed no information about this association.

The reporting odds ratio in the Lareb database supports a relationship between stomatitis and alendronate. In the WHO database, the use of all bisphosphonates as a group was disproportionally represented.

Some of the SmPCs already mention glossitis [8-10]. In literature, case reports were found about patients who kept the drug in their mouth before swallowing it. A direct irritating effect of bisphosphonates on the mucosa of the mouth can not be excluded. However, an immunity related reaction is also possible [15]. Such a mechanism could also explain stomatitis as mentioned in the SmPC of the intravenously administered zoledronate.

Conclusion

Stomatitis is not mentioned in the SmPC of bisphosphonates, except for the SmPC of zoledronate. Glossitis is mentioned in the SmPCs of risedronate, risedronate/calcium and etidronate/calcium. In case reports, a relationship between improper intake and stomatitis seems likely, and a specific warning for stomatitis caused by incorrect intake has been postulated. In one of the cases reported to Lareb, improper intake was mentioned. Therefore, stomatitis should be added to section 4.4 as possible result of improper intake.

For the other cases reported to Lareb, it is not clear how patients took their tablets. The number of reports and positive dechallenges support a causal relationship. Most cases are concerning the use of alendronate. The use of alendronate could be associated with stomatitis as ADR.

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