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Oral Mucosal Ulceration Induced by Alendronic Acid: A Case Series

Abstract: A number of medications may cause oral ulceration by either systemic or local mechanisms. Alendronic acid tablets, when in prolonged contact with the oral mucosa, are one such medication. When prescribing alendronic acid tablets, it is important to ensure that the patient is able to take them correctly and, if this is not the case, that alternative methods of bone protection are considered. When patients present with oral ulceration, it is important to consider whether a medicine could be causing a localized tissue reaction. This case series highlights three cases of alendronic acid-induced oral ulceration.

CPD/Clinical Relevance: Practitioners should be aware of the potential oral unwanted effects of medications, including oral ulceration induced by prolonged mucosal contact with alendronic acid.

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Bisphosphonates are used to manage a number of conditions including; the treatment and prevention of osteoporosis, bone metastases, multiple myeloma and Paget's disease of the bone.[1] Oral alendronic acid, the most commonly prescribed bisphosphonate used for the treatment and prevention of osteoporosis, acts to reduce bone resorption by inhibiting osteoclasts.[2] Well recognized adverse effects of bisphosphonates include; osteonecrosis of the jaw and external auditory canal, as well as atypical femoral fractures.[3] Alendronic acid is a frequently prescribed medication, with 8,758,501 prescriptions dispensed in the UK in 2015.[4] Dental practitioners therefore need to be aware of the potential oral and dental adverse effects of this medication, including oral ulceration. The following three cases describe oral ulceration caused by alendronic acid when left in contact with the oral mucosa for a prolonged period of time.

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Case series

Case 1

An 82-year-old female patient, referred by a local Oral and Maxillofacial Surgery unit, presented with a two-month history of oral blistering and crusting of the lower lip which had not responded to topical corticosteroids. There were no reported skin lesions or any previous history of oral ulceration. The patient had a complex medical history which included osteoarthritis, Stage 3 chronic kidney disease, Alzheimer's disease and a previous deep vein thrombosis. She was taking multiple medications including; chlorpheniramine, calcium carbonate, lactulose, paracetamol and codeine in addition to alendronic acid 70 mg tablets. The patient was a nursing home resident, who was unable to communicate or feed herself, used a wheelchair and attended the appointment with care staff. Her medication was administered by nursing staff. On examination, there was ulceration affecting the right side of the lower lip, demonstrating patches of inflammation interspersed with healing areas (Figure 1). In view of the unilateral site, details of drug administration, the patient's demeanour and following discussion with care staff, it was felt that the patient may have been pouching her medication in the labial sulcus. A provisional diagnosis of alendronic acid-induced oral mucosal ulceration was made. Subsequent haematological and serological assays (including indirect immunofluorescence) were negative and a biopsy was not undertaken.

The general medical practitioner (GMP) was asked to stop the bisphosphonate and consider alternative

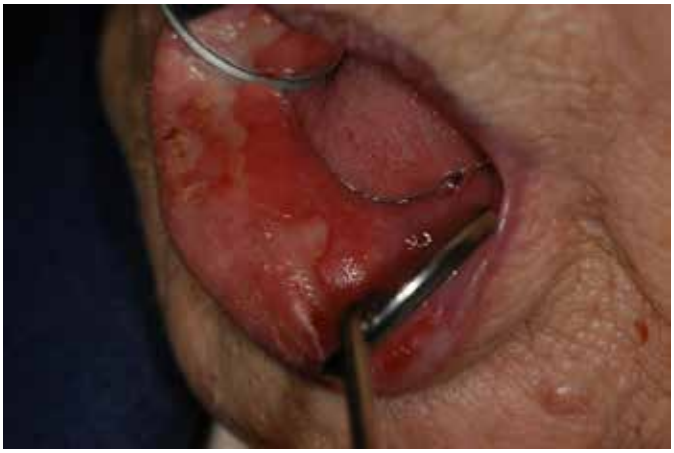

Figure 1. Case 1: Ulceration affecting the right side of the lower lip.

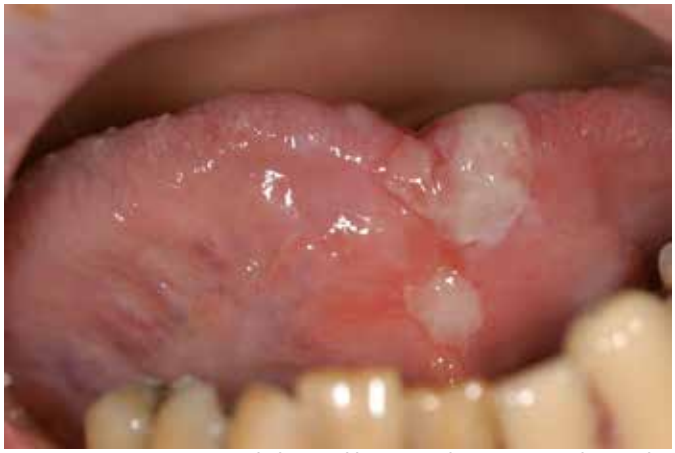

Figure 2. Case 2: Erosive and ulcerated lesion on the anterior and ventral aspects of the tongue.

bone protection. At review one month later the lip had completely healed.

Case 2

An 86-year-old female patient attended following referral from her general dental practitioner with mucosal lesions on the tongue and floor of the mouth. The patient's medical history included vascular dementia, epilepsy, polymyalgia rheumatica and transient ischaemic attacks. The patient was taking multiple medications, including 70 mg alendronic acid tablets, one tablet weekly, as well as calcium carbonate, sodium valproate, omeprazole, citalopram, prednisolone, lorazepam, docusate and senna. The patient was a care home resident and attended with staff from the home. On examination, there was an erosive and ulcerated lesion on the anterior and ventral aspects of the tongue (Figure 2). The differential diagnosis included ulcerative oral lichen planus, immunobullous disease, drug-induced ulceration or local trauma. The oral bisphosphonate was stopped and, at review one month later, healing was complete. Alternative bone protection was prescribed by the GMP.

Case 3

An 81-year-old female, accompanied by her granddaughter, attended having been referred by a local Oral and Maxillofacial Surgery unit with a 3-year history of recurrent lip crusting and ulceration. The patient had previously been prescribed antivirals for presumed herpetic lesions and corticosteroids for possible erythema multiforme without benefit. Blood tests, including a full blood count (FBC), liver function (LFT), urea and electrolytes (U&E) and serum immunoglobulins were normal. The patient took multiple medications including alendronic acid 70 mg tablets, one tablet weekly, as well as aciclovir, aspirin, atorvastatin, calcium carbonate, lactulose, macrogol, mirtazapine and paracetamol. She was a nursing home resident and had limited communication. On examination, there was extensive crusting and ulceration of the lower lip, extending intra-orally onto the dorsum of the tongue (Figure 3). It was noted that the patient postured her head to the left and that, as the ulceration appeared more prominent on this side of the lip and mouth, a local traumatic cause was suspected. The differential diagnosis included recurrent aphthous stomatitis, immunobullous disease, recurrent erythema multiforme or a drug-induced lesion. Further blood tests, including repeat FBC, LFT, U&E, as well as serum B12, folate and ferritin, were normal. Indirect immunofluorescence was negative. Following discussion with the GMP, the bisphosphonate was discontinued and topical 0.05% Fluocinonide ointment (Metosyn®, Reig Jofre UK Ltd, Devon, UK) in Orabase® paste (ConvaTec, Flintshire, UK), prepared locally by the hospital pharmacy, was prescribed. At a four week review the ulcer had healed with no further recurrence (Figure 4).

As suspected adverse drug reactions (ADRs), details of all three cases were reported to the Medicines and Healthcare products Regulatory Agency (MHRA) via the Yellow Card Scheme.[5]

Discussion

The above cases demonstrate the rare side-effect of oropharyngeal ulceration which can occur when alendronic acid tablets are chewed or allowed to dissolve in the mouth.[6] The directions for administration for alendronic acid state that it should be swallowed whole upon arising for the day with a full glass of water (not less than 200 ml). Patients should not crush or chew the tablet or allow the tablet to dissolve in their mouths because of a potential for oropharyngeal ulceration.[7] The authors' cases all occurred in patients diagnosed with dementia who retained oral alendronic acid tablets in their mouths, being unable to swallow the whole tablet immediately, resulting in a localized tissue irritation and subsequent ulceration. This is analogous to the condition known as an 'aspirin burn' which occurs when an aspirin tablet is placed directly onto oral soft tissues, often adjacent to a painful tooth, leading to chemical irritation of the oral mucosa.[8]

An electronic literature search undertaken using PubMed and Embase identified 12 additional reported cases of oral ulceration induced by oral bisphosphonates.[9-17] All cases involved the

Figure 3. Case 3: Extensive crusting and ulceration of the lower lip.

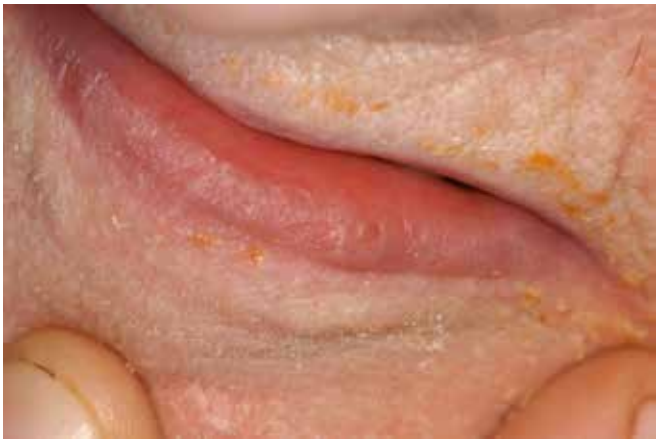

Figure 4. Ulcer from Case 3 healed.

use of alendronic acid tablets at a dose of 10 mg daily or 70 mg once weekly. Many of the patients had a learning disability or dementia and were residents in care facilities or required additional assistance in their homes. In all but one of the cases, the oral ulceration was caused by incorrect administration of the drug, with alendronic acid tablets either being habitually retained in the oral cavity before swallowing, or the patient being unable to swallow the tablet whole. In one case, the patient's nursing staff crushed the tablet and spooned the resultant powder into the labial sulcus. In another case, the tablet had been administered correctly yet ulceration still occurred.[15] In all cases, the ulceration resolved following cessation of alendronic acid or by correction of the administration technique.

Of interest, a case of labial mucosal ulceration attributed to intravenous zoledronic acid has also been reported.[18] This suggests that there may also be a systemic mechanism by which bisphosphonates can cause ulceration in addition to the topical effects seen with alendronic acid.

The mechanism of oral alendronic acid-induced mucosal oral ulceration has been attributed to direct tissue irritation, however, bisphosphonates have also been found to impair oral keratinocyte adhesion, differentiation and proliferation resulting in systemic effects on epithelial cells.[19] Similarly, zoledronic acid has been shown to inhibit proliferation and increase apoptosis in oral epithelial and fibroblast cells.[20] Nitrogen-containing bisphosphonates have demonstrated cytotoxic effects on various epithelial cells due to inhibition of cellular function action on the mevalonate pathway. This causes cellular apoptosis and growth inhibition.[2] It is also known that zoledronic acid has anti-angiogenic properties,[21] and that zoledronic acid and alendronic acid cause reduced production of angiogenic factors in osteoblasts.[22]

Evidence for oesophageal reactions includes a review that identified 199 cases of oesophagitis related to alendronate, of which 34 were considered serious or severe. Of those patients where information on both water intake and posture were available, 17 of 28 patients had either taken the medication with an insufficient volume of water or had not remained upright for the required time post-administration.[23] However, another study, did not find an increased incidence of oesophageal reactions when comparing patients taking oral alendronate with a placebo group.[24] The author suggested that this might be due to patients being followed-up on a regular basis, allowing for re-enforcement of dosing instructions to minimize the risk of incorrect administration. This would strengthen the argument that ulceration secondary to alendronate use is more likely to occur when the drug is administered incorrectly.

The MHRA's Yellow Card Scheme collects reports of side-effects and adverse incidents occurring due to medications or medical devices in the UK, as well as reports related to defective or counterfeit medical products.[5] A summary of all Yellow Card reports submitted for a drug can be obtained in the form of an Interactive Drug Analysis Profile. Up until 10 February 2016, the Yellow Card Scheme had received 50 reports of mouth ulceration, 8 reports of tongue ulceration and 3 reports of lip ulceration suspected to be associated with alendronic acid usage.

It is important to be aware of those patients who are at an increased risk of developing ADRs. All of the cases described in this article involved patients who were care home residents, had physical or mental disabilities and required their medication to be administered by care staff. A study in 2009 identified that 69.5% of UK care home residents had one or more errors in prescribing, monitoring, administration or dispensing of medicines.[25] Of these, 22.3% were incidences of drug administration errors. Whilst the paper assumed, probably correctly, that these vulnerable patients would likely have more medication errors if they lived in their own home, it highlights that there are still a significant number of errors made in relation to drug administration in care settings.

Conclusion

The potential for alendronic acid to induce oral ulceration is perhaps a less well known side-effect of the drug, however, the literature demonstrates that this usually occurs if the medication is incorrectly administered. Health and social care workers should be made aware of how to administer alendronic acid correctly, as well as being aware of patients who are more at risk of 'pouching' medication, such as those with

dementia, learning disabilities or neuromuscular conditions. Additionally, those professionals prescribing alendronic acid could consider alternative suitable methods of bone protection in such cases. The reporting of ADRs to the Yellow Card Scheme is encouraged to help monitor the incidence of such events and allow further action to be taken, if required.

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