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[The dental implications of bisphosphonates and bone disease](#) Australian Dental Journal, 2005; 50(Suppl.2):S4-S13

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The dental implications of bisphosphonates and bone disease

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Abstract

In 2002/2003 a number of patients presented to the South Australian Oral and Maxillofacial Surgery Unit with unusual non-healing extraction wounds of the jaws. All were middle-aged to elderly, medically compromised and on bisphosphonates for bone pathology. Review of the literature showed similar cases being reported in the North American oral and maxillofacial surgery literature. This paper reviews the role of bisphosphonates in the management of bone disease. There were 2.3 million prescriptions for bisphosphonates in Australia in 2003. This group of drugs is very useful in controlling bone pain and preventing pathologic fractures. However, in a small number of patients on bisphosphonates, intractable, painful, non-healing exposed bone occurs following dental extractions or denture irritation. Affected patients are usually, but not always, over 55 years, medically compromised and on the potent nitrogen containing bisphosphonates, pamidronate (Aredia/Pamisol), alendronate (Fosamax) and zoledronate (Zometa) for non-osteoporotic bone disease. Currently, there is no simple, effective treatment and the painful exposed bone may persist for years. The main complications are marked weight loss from difficulty in eating and severe jaw and neck infections. Possible preventive and therapeutic strategies are presented although at this time there is no evidence of their effectiveness. Dentists must ask about bisphosphonate usage for bone disease when recording medical histories and take appropriate actions to avoid the development of this debilitating condition in their patients.

Key words: Bisphosphonates, bone disease, avascular necrosis, jaws, dental treatment.

Abbreviations and acronyms: PEG = percutaneous endoscopic gastrostomy.

Aust Dent J 2005;50 Suppl 2:S4-S13

bisphosphonates have been found to be invaluable in controlling pain and preventing fractures.

In Australia, there were 2.3 million bisphosphonate prescriptions in 2003. This equals the number of amoxicillin prescriptions in the same year.¹ In 2004 this had increased to 2.5 million bisphosphonate prescriptions.¹ Generally the side effects of bisphosphonates are minimal. However, in 2003 there were sporadic case reports in the North American oral and maxillofacial surgery literature of patients with necrosis of the jaws following dental treatment.²⁻⁵ These patients were all receiving bisphosphonates, mainly pamidronate and zoledronate for the management of multiple myeloma, and bone metastases from breast cancer.

In South Australia, the Oral and Maxillofacial Surgery Unit of the Royal Adelaide Hospital managed five similar patients who were suffering from osteonecrosis of the maxilla and mandible in 2003.⁶⁻⁸ The patients' ages ranged from 57 to 84 years and comprised two females and three males. Three of the patients suffered from Paget's disease and two from multiple myeloma. They were undergoing treatment with either pamidronate or alendronate. Both medications are nitrogen containing bisphosphonates and have high affinity for bone tissue. From 2003 to June 2005 a further 10 cases were diagnosed, bringing our total experience to 15 patients.

The patients received a range of treatment from conventional non-surgical intervention to aggressive surgical re-section of the mandible and maxilla. Of the original group of five, two patients experienced pain relief after less than one year of treatment and three had ongoing chronic pain symptoms involving their jaws. This has recently been reported in the Australian medical literature.⁸ We are also anecdotally aware of similar cases elsewhere in Australia and are currently in the process of documenting this.

The discovery of the possible association between the bisphosphonates and osteonecrosis of the jaws prompted both the United States Food and Drug Administration and Novartis, the manufacturer of bisphosphonates used in cancer chemotherapy, to issue a warning to health care professionals in September 2004. The warning contained information about bisphosphonates and the risk of osteonecrosis of the jaw.⁹ These actions have been paralleled in Australia with an adverse drug reaction report in the medical literature¹⁰ and the publication by Novartis of guidelines for health professionals¹¹ and patients.¹²

Dental practitioners should be aware of the possible association between dental extraction and

INTRODUCTION

Bisphosphonates are a group of medications that have become increasingly and more widely used in the management of certain bone diseases (Table 1). Some of these conditions, such as osteoporosis, are very common, particularly in our ageing population. Metastatic bone disease as the end stage of breast or prostate cancer is common. Some conditions such as Paget's disease or fibrous dysplasia are less common but debilitating. In all of these conditions,

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Table 1. Dentists should mandatorily check the following points in all medical histories

Do you have any bone diseases?

- Osteoporosis
- Paget's disease
- Cancer with spread to the bones (breast, prostate, liver, lung and kidney)
- Multiple myeloma
- Other bone conditions

Are you taking any bisphosphonate medications?

<i>Nitrogen containing bisphosphonate</i>	<i>Non-nitrogen containing bisphosphonate</i>
Alendronate (Fosamax)	Etidronate
Risedronate (Actonel)	Clodronate
Pamidronate (Aredia, Pamisol)	Tiludronate
Zoledronate (Zometa)	

If positive to any of these questions, do not proceed to extraction or surgery without advice.

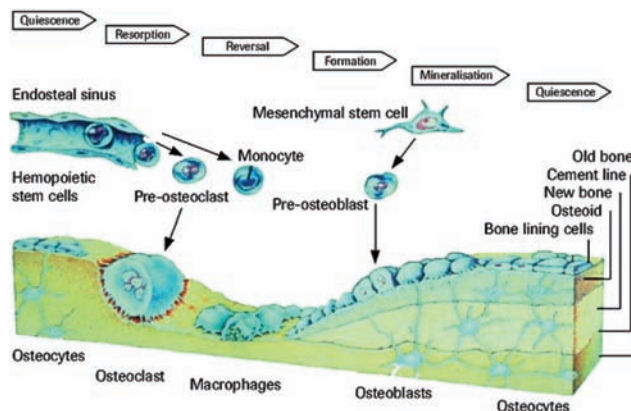


Fig 1. Normal bone physiology - Bisphosphonates affect angiogenesis, osteoclastic activity, osteoblastic activity and are incorporated in the bone matrix.

bisphosphonates, as bisphosphonates have become a standard medication in treating bone diseases. The dental management plan for these patients needs to be carefully formulated to minimize the risk of avascular necrosis of the jaws and allow for the overall health care of the patient to be maintained.

In this paper, we present a review of the bisphosphonates; the medical uses of bisphosphonates; osteonecrosis of the jaws; clinical case presentations; current prevention and therapeutic recommendations; and future directions.

Review of bisphosphonates

History

Bisphosphonates were initially formulated by scientists in the middle of the 19th century. They were first used in the textile, fertilizer and oil industries for the prevention of scaling in pipes because of their ability to inhibit calcium carbonate precipitation.¹³ Bisphosphonates were shown to have biological effects as they inhibit bone resorption. In high doses inhibition of ectopic and normal calcification can occur due to the physico-chemical inhibition of calcium phosphate crystal formation.^{13,14}

Chemistry

Bisphosphonates are synthetic compounds with a chemical structure similar to that of inorganic pyrophosphate, an endogenous regulator of bone mineralization. While pyrophosphate is comprised of two phosphate groups linked by phosphoanhydride bonds (P-O-P structure), bisphosphonates are comprised of two phosphonate groups linked by phosphoether bonds (P-C-P structure). This structure makes them more resistant to hydrolysis in acid conditions or by pyrophosphatases.^{15,16} The chemical structure of the basic bisphosphonate molecule renders it easy to modify and, therefore, the biological, therapeutic and toxicological characteristics of different generations of bisphosphonates vary dramatically.^{13,15}

Types of bisphosphonates

Currently, there are two main types of bisphosphonates: nitrogen containing and non-nitrogen containing. Most of the bisphosphonates available today are used for inhibition of bone resorption in the treatment of bone diseases (Table 1).

Bone physiology

Bone is a dynamic tissue that constantly remodels. The maintenance of healthy bone tissue relies on a balance between bone resorption and mineralization of bone matrix formation. The former is osteoclastic activity, the latter osteoblastic activity. Generally speaking, the older or non-functional bone is resorbed by osteoclasts and new bone formed by osteoblasts. The balance between these activities determines whether there is net bone formation or resorption (Fig 1).

Mechanisms of action

The mechanisms of action of bisphosphonates in bone metabolism are complex. Bisphosphonates act almost exclusively on bone when administered at physiological doses because of specific affinity to bone, where they deposit both in newly formed bone and in proximity to the osteoclasts. The half-life of bisphosphonates in the circulation is quite short, ranging from thirty minutes to two hours.¹⁴ However, once incorporated into bone tissue, they can persist for up to 10 years, depending on the skeletal turnover time.^{14,15} This prolonged skeletal retention can explain why single or short courses of intravenous injections can be effective for a long time in the management of Paget's disease.¹⁴

Bisphosphonates act on bone through several mechanisms simultaneously. For example, they can both decrease osteoclast activity and decrease osteoclast numbers. The first is exemplified by internalization by osteoclasts, causing disruption of osteoclast-mediated bone resorption,² the second by inhibiting osteoclast recruitment and accelerating

programmed cell death (apoptosis) of osteoclasts, thus reducing osteoclast numbers. Both mechanisms lead to reduction of bone resorption and to a decrease in bone turnover.¹³

The two families of bisphosphonates have different pathways via which they may act. Nitrogen containing bisphosphonates generally act through the mevalonate pathway but non-nitrogen containing bisphosphonates, such as etidronate, tiludronate and clodronate, are incorporated into the phosphate chain of ATP-containing compounds so that they become non-hydrolysable. The new P-C-P containing ATP analogues inhibit cell function and lead to cell death by apoptosis.^{13,16}

Of relevance to bone healing, Kapitola *et al.* reported bisphosphonates depress bone blood flow in rats and significantly decrease circulating levels of vascular endothelial growth factor which is important in the angiogenesis process.^{2,17,18}

In summary, bisphosphonates are non-metabolized analogues of pyrophosphate that are capable of localizing to bone and inhibiting osteoclastic function.^{19,20} Bisphosphonates bind avidly to exposed bone mineral around resorbing osteoclasts, resulting in very high levels of bisphosphonates in the resorption lacunae. Because bone-incorporated bisphosphonates are not metabolized, these high concentrations are maintained within bone for long periods of time.

Clinical uses

One of the early clinical uses of bisphosphonates was as bone scan imaging agents. They remain very useful for detecting bone metastases and other bone lesions. Bisphosphonates are now used as the treatment of choice for inhibition of bone resorption in diseases where no effective treatment previously existed.

Paget's disease is a common, non-metabolic disease of bone of undetermined aetiology. It usually affects the middle-aged and elderly. It is initially characterized by excessive bone destruction but this is followed by unorganized bone repair and remodelling. The condition is mostly asymptomatic but some patients may present with bone pain and pathological fractures, and the bisphosphonates control this.¹⁵ Bisphosphonates also play a role in the management of osteoporosis, a common disorder characterized by abnormal rarefaction of bone. Osteoporosis occurs most frequently in post-menopausal women but can also affect males. The condition is also common in immobilized individuals and patients who are on long-term steroid therapy. The principal effect is to predispose individuals to pathological fracture with consequent pain and disability.²⁰

Hypercalcemia is usually a result of excessive bone resorption and release of calcium into the circulation. It is secondary to bony metastatic malignancy, hyperparathyroidism, or a humoral effect of neoplasia. Patients can present clinically with confusion, anorexia, abdominal pain, muscular pain and weakness. If

untreated it may progress via dehydration to renal failure and death. Bisphosphonates rapidly normalize serum calcium levels in most patients, irrespective of the underlying aetiology.

Bisphosphonates effectively reduce the complications of the malignant osteolytic process. They reduce bone pain, the incidence of hypercalcemia and pathologic fracture, and the need for palliative radiotherapy. Multiple myeloma is a primary malignant neoplasm of the bone marrow. The tumor is composed of neoplastic plasma cells which destroy the osseous tissue, especially in flat bones such as the ribs, skull and pelvis. The use of bisphosphonates significantly improves the management of multiple myeloma.¹⁵ Overall, bisphosphonates improve the quality of life of patients suffering from abnormal bone resorption by reducing the number of pathological fractures and bone pain.

Osteonecrosis of the jaws

Since the initial reports^{2,4-8} there has been considerable interest in this new variant of osteonecrosis associated with bisphosphonates. The similarity of bisphosphonate-related osteonecrosis of the jaws to the historical entity of phosphorous necrosis or 'phossy jaw' has been noted.²¹ In the mid-19th century match making workers suffered severe jaw pain which was initially diagnosed as toothache. Extractions made the condition worse, with a non-healing socket, sequestration, pain, offensive smell, soft tissue infections and deformity.²² The condition persisted for years and there was a mortality rate of 20 per cent from spreading infection. It was eventually determined that this condition was associated with industrial contact with white phosphorous. Cases of 'phossy jaw' continued into the 20th century, mainly in workers in the munitions industry. 'Phossy jaw' was eventually eradicated by changes in industrial hygiene.

In the early 20th century similar cases of jaw necrosis were seen in workers applying radium to watch and instrument dials to make them luminescent.²³ This too was eradicated by changes in industrial hygiene. Currently, osteonecrosis of the jaws is secondary to radiotherapy for head and neck cancer. Initially osteoradionecrosis was thought to be bacterial. It is now thought to be secondary to avascularity of the bone. Treatment protocols involve hyperbaric oxygen and surgical re-section.²⁴

Initially, the first diagnosed cases of bisphosphonate necrosis were treated with similar techniques as for osteoradionecrosis.^{8,24} These techniques failed to be effective as bisphosphonates involve the whole jaw bone and indeed all of the skeleton whereas radiotherapy affects only the localized field. With osteoradionecrosis there is a reservoir of unaffected bone in the area which can respond.

The histological appearance of 20 samples of bisphosphonate affected bone has been reported.²¹ Generally, the bone showed reduced osteoclastic and reversal line activity. The vascularity of the connective tissue was intact but congested with red blood cells.

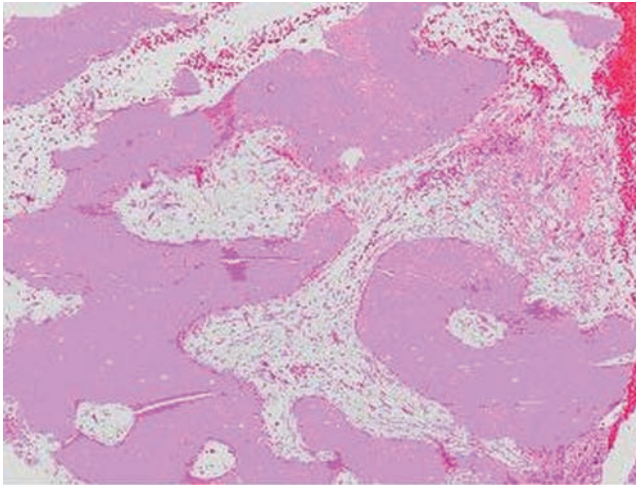


Fig 2a. (Case 7) Low power photomicrograph showing irregular but largely vital bone trabeculae composed of 'old' and 'new' bone matrix and focally and chronically inflamed stromal connective tissue. The microscopic picture in this area is one of low grade non-suppurative chronic osteomyelitis. Original magnification x 40. H&E.

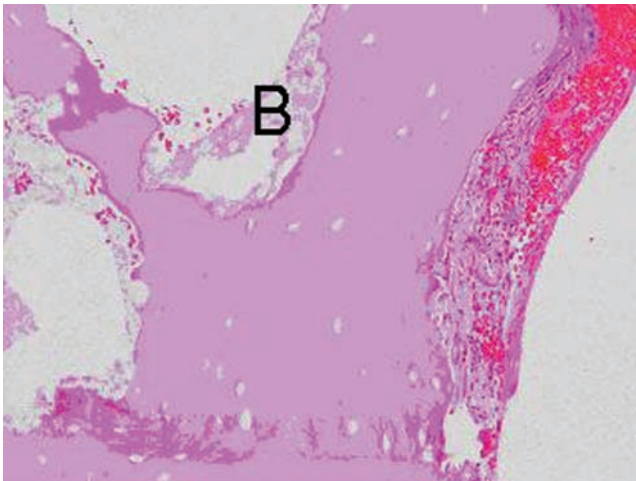


Fig 2b. (Case 7) Photomicrograph showing non-vital bone with empty osteocyte lacunae and prominent evidence of osteoclastic resorption. The bone shows evidence of bacterial colonization (B). Original magnification x 100. H&E.

Bacterial colonies surrounded by inflammatory cells were prominent. These findings are similar to those noted in our cases (Figs 2a and 2b).

The maxillary bone of two cases were analysed by back-scattered electron imaging to measure the degree of bone tissue-level mineralization and the number of osteocyte lacunae in the mineralized bone tissue. One 78-year-old female (Case 4) with Paget's disease, treated with pamidronate 90mg IV monthly for 18 months, showed high bone tissue-level mineralization, greater than the 95th percentile of adult proximal femoral bone. The mineralization was associated with a reduced number of osteocyte lacunae in the bone indicative of necrosis in some regions of the biopsy. One 75-year-old female (Case 7) with multiple myeloma, treated with pamidronate 90mg IV monthly for four years, was slightly less mineralized than the case above but still highly mineralized and associated with active resorption. The active resorption perhaps

contributed to the slightly lower level of mineralization and an apparent normal number of osteocyte lacunae in the presence of osteomyelitis. In both cases, the bone samples were obtained whilst the patients were surgically treated for severe soft tissue infections. Further quantitative bone analysis and comparison with control jaw bone samples are necessary to understand the significance of these observations.

Current aetiologic possibilities for bisphosphonate necrosis are centred upon the effects of bisphosphonates on the inhibition of angiogenesis¹⁸ and osteoclastic action.²⁵ It is also not known whether the jaw bones metabolize bisphosphonates in the same way as the long bones.

It is uncertain if the the term avascular necrosis is correct, although it has been widely used. Does the bone die because it loses its vascularity or does it die then lose its vascularity? Similarly, bisphosphonate osteomyelitis implies an inflammatory pathogenesis. For these reasons the term 'bisphosphonate osteochemonecrosis of the jaw' has been suggested.²¹ However, this is a very long name and 'bis-phossey jaw' has a simple and historical attractiveness.²¹

Clinical cases

The first five cases treated by the South Australian Oral and Maxillofacial Surgery Unit have been published previously.⁸ All patients remain alive and under regular review. The previously presented cases are updated in Table 2.

Subsequent cases treated by the Unit are presented in Table 3 and all patients are summarized in Table 4. The most striking features were that these patients were generally older, medically compromised patients with ongoing debilitating jaw pain. Weight loss was a problem and two patients required percutaneous endoscopic gastrostomy (PEG) feeding. Once established, the neck and jaw infections could not be eliminated as it was not possible to remove the cause, the dead jaw.²⁶ Hence they recurred and could only be controlled by intermittent antibiotics. One patient required a tracheostomy to control her airway. Of the three who resolved in less than one year, all were on alendronate. Two of the three cases of osteoporosis were in the resolved group. Two severe longstanding patients have resolved after 2+ years. Nine of 15 are ongoing.

Dental implications

The discovery of the possible association between bisphosphonate therapy and avascular necrosis of the jaws is relatively recent and our current understanding of the process is limited. From the recent literature from Australian,⁸ North American,^{2,4,5,11,19} Singaporean²⁷ and Canadian²⁸ sources, bisphosphonates appear to be a direct factor in a multifactorial aetiology leading to avascular necrosis in the jaws. It has been suggested that the bisphosphonates produce ischaemic changes in the maxilla and mandible. The fact that these

Table 2. Clinical details of five patients with avascular necrosis of the jaw in South Australia, 2003^a

Case	Age, Sex	Presentation	Precipitant	Bisphosphonate (indication)	Other medications	Treatment	Outcome 2003	2005 status
1	57, M (Fig 3)	Painful exposed bone in maxilla and mandible	Tooth extraction	Pamidronate (90mg IV monthly for 6 years) (Multiple myeloma)	Dexamethasone, methotrexate, warfarin, folic acid, ranitidine, metformin, hydroxychloroquine, verapamil, sertraline, morphine	Hyperbaric oxygen, Le fort I level maxillectomy, bisphosphonate continued	Persistent necrosis of midface and mandible. PEG feed.	No pain Feels well Large defect
2	64, M	Ulcer R hard palate with bone sequestrum	Tooth extraction	Pamidronate (90mg IV monthly for 2 years) (Multiple myeloma)	Prednisolone, cyclosporine, itraconazole, sulfamethoxazole-trimethoprim, ranitidine, penicillin	Sequestrectomy, local debridement, bisphosphonate continued	Resolution	Resolution
3	73, M	Pain, swelling anterior maxillary alveolus	Tooth extractions	Alendronate (40mg orally daily for 5 years) (Paget's disease)	Amlodipine, tramadol, perindopril	Local debridement, sequestrectomies, primary flap closure, bisphosphonate ceased	Resolution	Resolution
4	78, F	Painful exposed bone in maxilla	Denture pressure	Pamidronate (90mg IV monthly for 18 months) (Paget's disease)	None. Initially reported ^d as no other medications but has significant non-medication problems • Pharyngeal SCC Surgery and RT • Pneumonia	Hyperbaric oxygen, local debridement, denture reline, bisphosphonate ceased	Persistent areas of exposed bone	2 major episodes of infection. Weight loss. PEG
5	84, F	Non-healing extraction site in left maxillary alveolus	Tooth extraction	Pamidronate (60mg IV monthly for 6 months) (Paget's disease)	Diltiazem, simvastatin, ferrous sulphate, aspirin, bendrofluazide	Wide intra-oral re-section with primary flap closure, bisphosphonate ceased	Persistent fistula	Persistent fistula, intermittent antibiotics

complications were not recognized during the trial phase of these drugs suggests that the effect of the drugs when they become incorporated in the bones might be cumulative in nature. A recent study of multiple myeloma patients treated with zoledronate acid showed a progressively increasing incidence of osteonecrosis of the jaws to 10 per cent by 36 months. With pamidronate the incidence was lower to four per cent by 36 months.²⁹

The unique environment of the oral cavity could explain why the maxilla and mandible are solely involved. It can be hypothesized that patients who have received long-term bisphosphonate therapy may have a compromised blood supply to their maxilla and mandible. When dental extractions are performed on this group of patients, the open bony wound with a compromised healing ability cannot cope with the presence of oral microflora.²⁸ The extraction wound then becomes infected and progresses into osteomyelitis due to the poor healing ability of the tissues. It then develops into osteonecrosis.²⁸ It should be noted that all other bones in the skeleton are well enclosed in the soft tissue and thus protected from a resident microflora.

Clinical management

Medical practitioners treating bone disease with bisphosphonates need to be aware there is a small risk their patient may develop the painful, debilitating and

difficult to treat condition of 'bis-phossy jaw'. The indication and bisphosphonate regimen used needs to be carefully considered. The need for the patient to be dentally fit and prepared to maintain this state for life should be part of the informed consent for treatment. Given the clinical benefit^{22,24} there is no need to withdraw bisphosphonates from the market. However, legal aspects have already been raised in the US.³⁰

As the Australian population ages, dental management of dentate patients undergoing bisphosphonate therapy will become a common issue. It can be divided into preventive and therapeutic management.

Preventive recommendations

A comprehensive recent medical history is essential before commencing any dental treatment. Identifying the risk factors in the medical history is mandatory and will help the patient's overall well-being and safety. Patients taking potent bisphosphonates for more than one year, particularly for bone conditions other than osteoporosis, and those on concomitant steroids appear to be at highest risk of developing 'bis-phossy jaw'. Other factors that appear to further increase the risks include: residual multiple myeloma or another malignancy; hypoproteinemia; renal impairment from disease or drugs; and/or chemotherapy.

The treatment plan for a patient who has been on bisphosphonate therapy should involve restorative

Table 3. Clinical details of patients seen in South Australia 2004-2005

Case	Age, Sex	Presentation	Precipitant	Bisphosphonate (indication)	Other medications	Treatment	Outcome
6	72, M	Non healing extraction sockets maxilla	Tooth extraction	Alendronate 40mg weekly for 3 years (Osteoporosis)	Nil	Mouth rinses	Resolved
7	75, F (Fig 1)	Submandibular swelling and exposed left mandible	Tooth extraction	Pamidronate 90mg IV monthly for 4 years (Multiple myeloma)	Thalidomide 100mg daily	Local debridement, severe soft tissue infections x 3. Tracheotomy	Ongoing, (Severe infections)
8	69, M	Exposed right and left mandible	Tooth extraction	Alendronate 40mg weekly for 6 months (Paget's disease)	Diabex, noten, lipex, kapanol, calcitonin, tryptanol	Local debridement, mouth rinses	Ongoing Low grade infection
9	82, F	Exposed mandibular surface with pus drainage and cutaneous fistula	Tooth extraction	Pamidronate (90mg IV every 3 months for 5 years) Alendronate (20mg orally daily, 1 year) (Paget's disease)	Thyroxine NSAIDS	Declined treatment, antibiotics for fistula	Ongoing - Draining fistula - Lost 32kg - Declined for 2+ years
10	72, F (Fig 4)	Submental abscess, exposed right mandible	Tooth extraction	Pamidronate 90mg IV for 3 years (Multiple myeloma)	Thalidomide 100mg daily	Mouth rinses	Ongoing - 1 severe infection - ongoing treatment - endodontic treatment
11	39, M	Oroantral fistula with pus discharge	Tooth extraction	Alendronate 40mg weekly for 1 year (Osteoporosis)	Nil	Mouth rinses	Resolved
12	78, M	Painful maxilla in anterior and posterior region	Tooth extraction	Pamidronate (Metastatic prostate cancer)	Rani-2, iscover, pexsig, cardizem, digoxin, tofranil	Local debridement	Ongoing review, large maxillary bony defect
13	58, M	Painful non healing right mandible	Tooth extraction	Pamidronate (for 8 years) (Multiple myeloma)	MS-Contin, baclofen, zolofit	Local debridement Primary closure after 18 months	Deceased of acute bone bone marrow transplant rejection
14	58, F (Fig 4)	Painful right mandible	Deep bony impacted wisdom tooth removal	Alendronate 40mg weekly started after tooth removal (Osteoporosis)	Bactrim, Alendronate Neurontin, endep	Non surgical management	Ongoing review. Patient has lost 10% body weight in 10 months
15	74, M	Painful left mandible	Tooth extraction	Zoledronic acid 3 years (Metastatic prostate cancer)	Anandron, calcitriol, digoxin, dexamethasone, warfarin, frusemide, omeprazole	Non surgical management. Endodontics	Ongoing treatment

Table 4. Summary of all Adelaide cases to date

No.	Age (median range)	Sex	Involved jaw	Precipitant	Bone disease	Bisphosphonate	Treatment	Other medications	Complications*	Outcome
15	69 (34-84)	9M 6F	Maxilla 8 Mandible 6 Both 1	Tooth extraction 14 Denture irritation 1	Multiple myeloma 5 Paget's disease 5 Bone cancer 2 Osteoporosis 3	Pamidronate 8 Alendronate 5 Pamidronate and Alendronate 1 Zoledronate 1	HBO and re-section 1 HBO and curettage 1 Curettage 6 Non-surgical only 6	Yes 13 Nil 2	Large defect 2 Persistent fistula 1 Serious infection 4 Feeding difficulty 4 No major complications 8 *some multiple	Ongoing 9 Resolved <1 yr 3 Resolved <2 yr 2 Died other cause 1

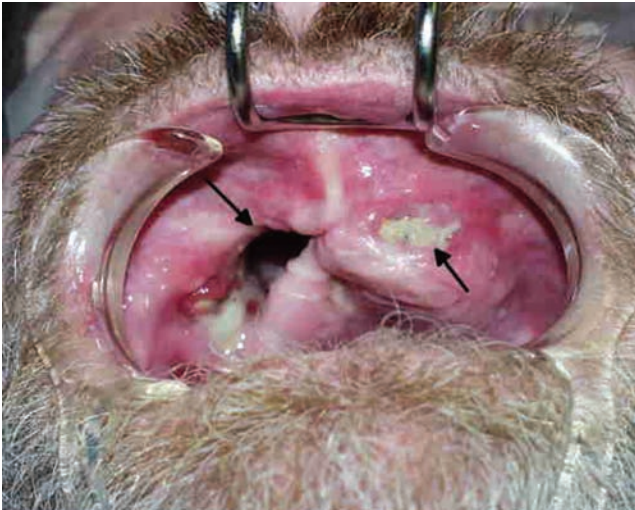


Fig 3a. Case 1. Clinical appearance 2003, following right maxillary extractions. Right maxillary necrotic area (long arrow) left sequestrum (short arrow).



Fig 3c. Clinical appearance 2005. Tissue healthy, no pain. No obturator but eats soft food via mouth. Had a percutaneous endoscopic gastrostomy (PEG) feeding for 18 months.

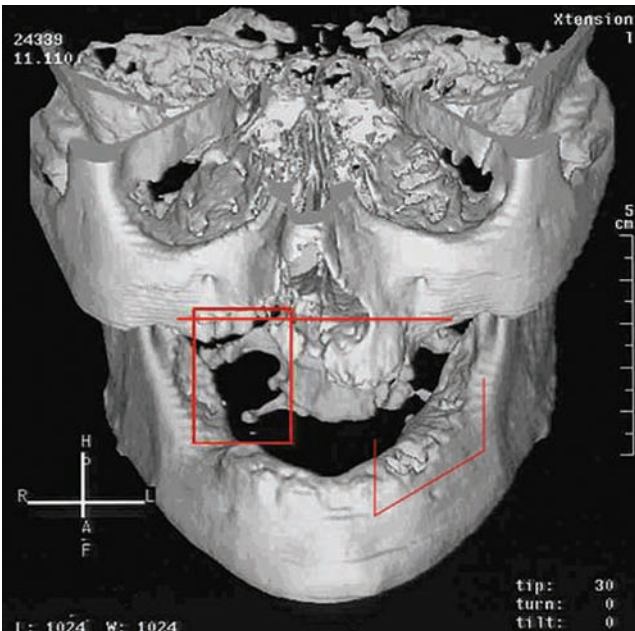


Fig 3b. CT maxilla and mandible 2003, post extraction and prior to re-section. Lines show level of maxillectomy and subsequent left mandibulectomy.

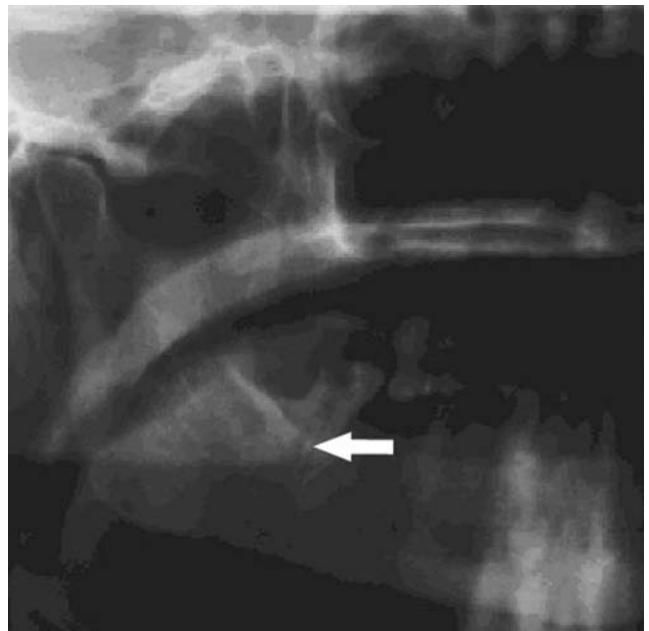


Fig 4a. Case 10. OPG radiograph 2003, just prior to extraction of tooth 46. Socket did not heal but patient did not represent for treatment. Arrow points to dense interseptal bone.

dentistry, limited non-surgical periodontics and endodontics to control dental decay, periodontal disease and periapical inflammation. Patients who have dentures should have well maintained soft liners to minimize trauma to the oral mucosa or leave their dentures out. Failing soft liners would be more irritating than a hard but smooth denture. Extraction and all types of surgery should be avoided. If an extraction is mandatory, for example an infected vertically split tooth, then the tooth should be extracted with minimal bony damage or exposure. Although there is no research to validate it, prophylactic antibiotics³¹ and suturing the socket to close the wound are advised. As a novel approach the authors have been using orthodontic elastic bands to exfoliate teeth. This results in a slow extraction over a few weeks which

allows the oral mucosa to migrate down the tooth as it exfoliates so there is no open wound.³²

There are conflicting reports regarding dental implants. Experimental studies show a positive effect of bisphosphonates on the bone around implants in experimental animals^{33,34} and humans.³⁵ Failure of osteointegration in a patient who had successfully integrated implants but then commenced on bisphosphonate therapy has been reported.³⁶ Current advice is that placement of implants is best avoided if the patient has serious bone disease and are on potent doses. Osteoporotic patients on lower doses need a full informed consent before proceeding. Patients on bisphosphonate therapy with existing implants should be regularly clinically and radiographically monitored. Increased bone density around the implant, similar to



Fig 4b. OPG 2005. Dense bone at the extraction site with two dense spicules which look like tooth roots. (Arrow) These are a thickening of the periodontal lamina and are present on the 2003 OPG (Fig 4a).



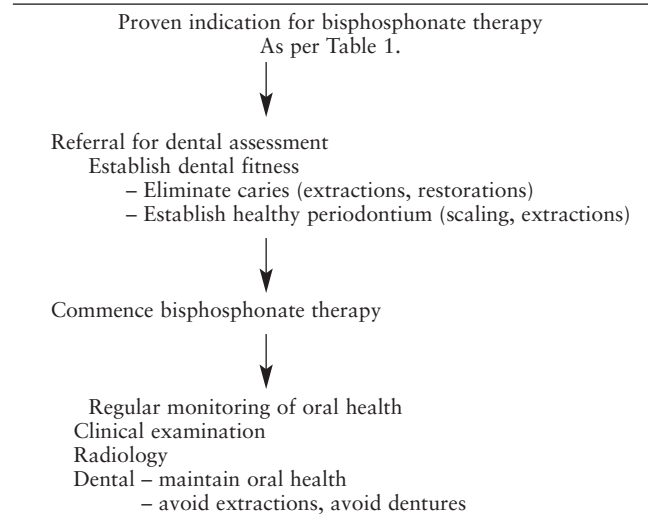
Fig 4c. Intra-oral view 2005. Exposed bone right alveolus. (Arrow) Remaining teeth poor. Teeth with necrotic and infected pulps with apical periodontitis have been treated endodontically.



Fig 4d. Presented in early 2005 with acute submandibular infection and draining sinuses. Treated with drainage and antibiotics. Much improved but draining fistulae continue.

that shown around the socket in Fig 4c, may occur. If bone pain or loss of integrity occurs the superstructure should be removed and the implant left submerged. Bone surgery must be avoided as the bone is exceedingly dense and avascular necrosis may occur.

Table 5. Preventive strategy for dental management of patients about to start bisphosphonates

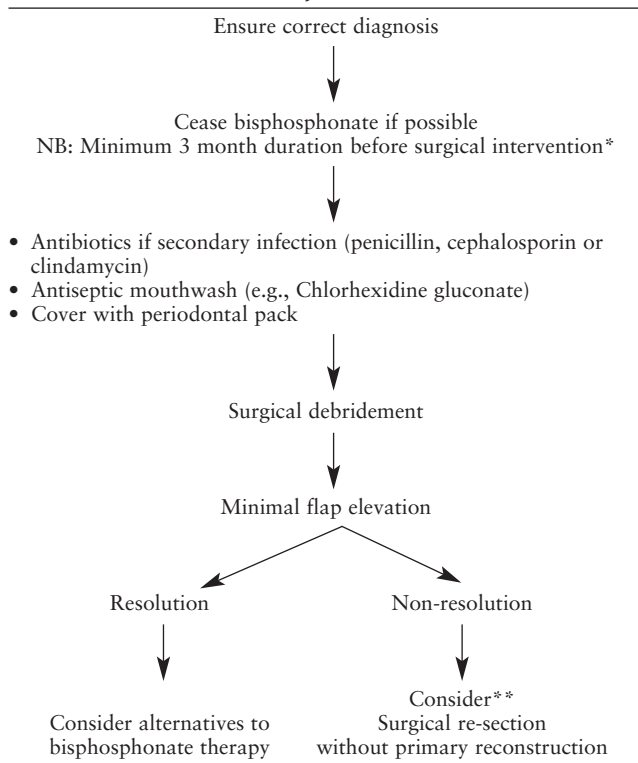


Full dental assessment and treatment planning should occur prior to the patient commencing bisphosphonate therapy (Table 5). If the bisphosphonate therapy can be delayed without the risk of other skeletal related complications, teeth with a poor prognosis should be extracted and all surgical procedures completed before the commencement of the bisphosphonate therapy. The decision to withhold the bisphosphonate therapy should be made by the treating physician in consultation with an oral and maxillofacial surgeon and dentist. Once bisphosphonate therapy is commenced, regular dental monitoring of oral health and a preventive approach should be adopted. Patients should be educated regarding good oral hygiene practice and report any symptoms. Treating medical specialists, oncologists and endocrinologists prescribing these drugs should perform a brief oral exam during follow up appointments and refer as appropriate.¹¹

Therapeutic recommendations

The first step is to establish the diagnosis if a patient on bisphosphonate therapy presents with a non-healing oral wound. This requires an accurate medical and dental history. Patients with diabetes, radiotherapy in the head and neck region and immunocompromised patients can have delayed wound healing. Once the diagnosis of 'bis-phossy jaw' is made the treating medical practitioner, oral and maxillofacial surgeon and dentist need to confer to establish a management plan. At present there is no simple single effective treatment for 'bis-phossy jaw'^{2-5,8,11} The first approach should be non-surgical with the use of antiseptic mouth rinses and antibiotics to prevent or treat secondary infection. Removable appliances lined with a periodontal pack that passively cover the bony defect can be inserted to protect the site from further trauma and may aid mucosal covering of the exposed bone.^{8,11} This is a slow process.

Table 6. Therapeutic management of established avascular necrosis of the jaws



*It is probable that this time span is too short.
**Extreme caution is recommended at this point.

If the exposed bone is painful or there is significant secondary infection, localized surgical debridement without primary reconstruction can be considered. Minimal mucoperiosteal flap reflection to preserve the blood supply to underlying bone should be used. The problem is that the whole skeleton is involved. Resection to a normal bleeding bone margin cannot be undertaken as for osteoradionecrosis. Bone grafting, either as a free graft or by microvascular transfer, involves affected bone. There is a risk that there could be two problem areas, the donor graft site as well as the recipient jaw site. Major re-section surgery should be avoided if at all possible.^{2,4,5,8,11}

In summary, for established cases it is recommended that treatments begin with the recognition that palliation and control of secondary infection are the primary goals. Control of progression has been obtained in most cases with long-term or intermittent courses of a penicillin or second generation cephalosporin, chlorhexidine mouthwash and periodic minor debridement of soft-textured sequestering bone and wound irrigation (Table 6).

Future directions

There are many unknowns regarding the process of bisphosphonate-related osteonecrosis of the jaws. The precise pathophysiology is unknown. The incidence is currently low, probably of the order of 0.1-1 per cent of all patients on bisphosphonates. The incidence may differ between different bone pathologies, different bisphosphonates and different dosage regimens. The



Fig 5a. Case 14. Resorbing horizontally impacted 48, uneventfully removed in 2003. The patient was commenced on alendronate for osteoporosis after the extraction.



Fig 5b. Bone pain right mandible. OPG 2005. 48 socket appears normal, tooth 47 has a clinically normal pulp.

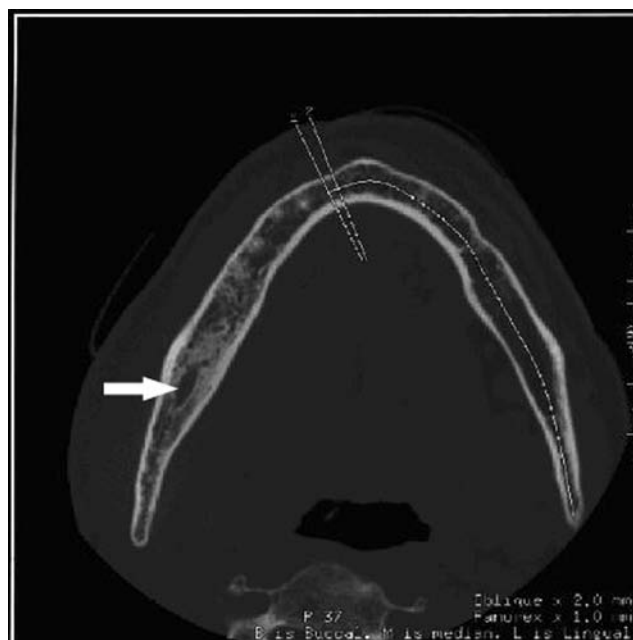


Fig 5c. CT scan mandible shows no bony infill of the socket (Arrow) but dense mineralization around socket.

most concerning question is whether this is a cumulative problem. If bisphosphonates do continue to accumulate within the bones until a threshold dose is

reached then the incidence of 'bis-phossy jaw' will increase.²⁹ The authors have established a number of trials with the Bone and Joint Research Laboratory of the Institute of Medical and Veterinary Science and Multiple Myeloma and Paget's disease clinics within the Royal Adelaide Hospital, University of Adelaide Health campus, in an attempt to answer these questions. All the cases in Australia treated by oral and maxillofacial surgeons are also being documented.

An interesting but unresolved question is to how best to extract teeth in patients on bisphosphonates. Currently, there is no evidence for the clinical suggestions on extraction for patients on bisphosphonates. The problem with such studies is that as the risk is low a large study is required to obtain statistical significance. If one variable – for example simple forceps extraction versus elastic band exfoliation – is better, then assuming a 1 per cent risk of osteonecrosis to get to a p<.05 significance, a trial of at least 2000 patients all on bisphosphonates and all requiring extractions is needed!

There are important dental implications with patients on bisphosphonates for bone disease but the best practice answers are currently unknown.

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