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The Surgeon, Journal of the Royal Colleges of Surgeons of Edinburgh and Ireland

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Review

Bisphosphonate osteonecrosis of the jaw: A historical and contemporary review

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ARTICLE INFO

Article history:
Received 13 July 2011
Received in revised form
31 August 2011
Accepted 6 September 2011
Available online 7 October 2011

Keywords:
Bisphosphonate
Osteonecrosis
Mandible
Maxilla
Dentistry

ABSTRACT

The use of bisphosphonate drugs has been popularised in the late 20th century for the management of many conditions associated with abnormalities of bone turnover, particularly metastatic and haematogenous malignancy and osteopenia. The increase in indications for the use of bisphosphonates was supported by what was thought to be a very good safety profile. However in 2003 cases of osteonecrosis related to the use of bisphosphonates were first described.

The pathogenesis, and with this the explanation of why it only appears to affect the maxillofacial skeleton, and the best way of managing this problem remains unknown.

In this review we examine the process of identification of this pathology and the development of guidelines from medical societies and professional bodies on the management of patients before commencing bisphosphonate therapy, requiring dental treatment whilst on therapy, or with a diagnosis of bisphosphonate associated osteonecrosis of the jaws.

Bisphosphonate drugs

Bisphosphonates (BP) are pyrophosphate analogues, which share a common phosphorous–carbon–phosphorous chemical core. These compounds have been synthesised, and used in industry since the 19th century but it is only in the 1960s that their in-vitro ability to inhibit the precipitation of calcium phosphate was applied clinically.[1] Their principal action is to inhibit resorption of bone, which results in an increase in the mineral density of bone and a reduction in serum calcium.[2]

They are poorly absorbed by the gastrointestinal tract (absorption of ingested dose is only in the order of 10%) and excreted largely unchanged by the kidneys. BPs have a high affinity for exposed hydroxyapatite within bone mineral and within bone are metabolically inactive.[2] As the process of metabolic bone resorption progresses, previously bound BP is released and exerts their clinical effect.[1]

There are two classes of BPs which have different mechanisms of action on osteoclasts based on the presence or absence of a nitrogen side chain on the pyrophosphate group. Non-nitrogen containing BPs are taken up by the osteoclast and antagonise the cellular energy pathways leading to cell apoptosis. Nitrogen containing bisphosphonates have a more complex pathway of action where they inhibit the mevalonate

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1479-666X/$ – see front matter
doi:10.1016/j.surge.2011.09.002

pathway which affects the osteoclastogenesis, apoptosis and cytoskeletal dynamics.[1] Zoledronate has also been shown to inhibit human endothelial cell proliferation and to modulate endothelial cell adhesion and migration.[3] The antitumour effect of bisphosphonates is thought to be due to induction of tumour cell apoptosis, and inhibition of tumour cell adhesion and invasion.[4]

They were originally licensed for the management of skeletal complications of malignancy, including advanced breast cancer and multiple myeloma. The efficacy of BP in controlling adverse skeletal events coupled with their apparently low incidence of adverse events led to a rapid increase in their use and gradual widening of the approved indications to include the management of hypercalcaemia of malignancy, Paget's disease of bone, osteoporosis and osteogenesis imperfecta.[1,2]

Although the use of BP in the management of periodontal disease and conditions associated with heterotrophic calcification has been reported, their use in this regard has been largely abandoned because of lack of clinical effectiveness and side effects.[1,5]

A list of BP available for prescription in the UK is shown in Table 1.

History of bisphosphonate associated osteonecrosis of the jaw (BONJ)

Osteonecrosis of the jaws may be associated with a number of different predisposing conditions, with its pathophysiology varying with the predisposing factors.

The risk of osteonecrosis associated with phosphorous compounds was first described in the 19th century in workers in the matchmaking industry who presented with pain, exposure of the jaw bone and infection associated with sequestration. The term 'phossy jaw' was coined for these patients, who often followed an indolent but progressive course, and in this pre-antibiotic era the mortality was high.[6] The gradual disappearance of this condition has been related to reduced use of white phosphorous in industry and improved working conditions.

Ulceration of the oral mucosa as a complication of oral BP therapy was described in 1999 but this was thought to be due to direct mucosal injury, similar to oesophageal ulceration, another recognised side effect of alendronate and BONJ was not in fact reported in any of the clinical trials on BP.[7,8]

In the first few years of the 21st century cases of osteonecrosis where no other cause could be identified were seen in a number of institutions, and the link with BP drugs first considered.[9] Subsequently osteonecrosis associated with the use of bisphosphonates was presented at scientific meetings and published in the literature in 2003 by groups in Fort Lauderdale, Miami and New York,[10–13] Interestingly, in the same edition of the Journal of Oral & Maxillofacial Surgery that Marx published a letter to the editor reporting this complication, a series of patients was reported by Wang et al which they related to chemotherapy but who all in fact were receiving pamidronate.[14] Since then there has been a large number of publications in the scientific literature on BONJ.

As more cases were reported to the Food and Drug Administration, committees were established with the pharmacology industry to examine this problem. In 2004 letters were sent out to clinicians and the drug packaging information changed to include the possibility of osteonecrosis of the jaw. Following a retrospective review of cases in clinical trials of Zometa and Aredia reported to the FDA it was suggested that BONJ did occur but was not identified as such. (Background information of Oncological Drugs Advisory committee meeting March 4, 2005. www.fda.govohrms/dockets/05/briefing/2005-4095B2_02_01-Novartis-Zometa.)

In 2006 the Medicines and Healthcare Regulatory Authority in the UK first published guidance on BONJ in its 'Current problems in pharmacovigilance' newsletter (Available at www.mhra.gov.uk). This stated that "A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors (e.g. cancer, chemotherapy, corticosteroids and poor oral hygiene). While on treatment, patients with concomitant risk factors should avoid invasive dental procedures if possible."

Also in 2006 the Chief Dental Officer wrote to all general dental practitioners alerting them to the potential oral health and dental care impact of the use of BP medication (available www.doh.gov.uk, reference number 6467).

This information has been updated, albeit largely unchanged following reports from the European Commission on Safety of Medicines and updated reviewing of the literature. (European Medicines Agency. Opinion of the committee for medicinal products for human use pursuant to article 5(3) of regulations (EC) No 726/2004 on bisphosphonates and osteonecrosis of the jaws. Available www.emea.europa.eu.)

Diagnosis of BONJ

One problem in identifying cases of BONJ is that there is no universal agreement on a definition of the condition, compounded by the many terms used to describe it; BP associated

Table 1 – Bisphosphonates available within the United Kingdom.

Drug Name	Trade Names	Routes of Administration
Alendronic Acid[a]	Alendoronic Acid	Oral
	Fosamax	Oral
	Fosavance	Oral
Sodium Clodronate	Bonefos	Oral
	Clasteon	Oral
	Loron 520	Oral
Disodium Etidronate	Didronel	Oral
Ibandronic Acid[a]	Bondronat	Oral, Infusion
	Bonviva	Oral
Disodium Pamidronate[a]	Disodium Pamidronate	Infusion
	Aredia	Injection
Risedronate Sodium[a]	Actonel	Oral
Tiludronic Acid	Skelid	Oral
Zoledronic Acid[a]	Aclasta	Infusion
	Zometa	Infusion

a Nitrogen containing bisphosphonate.

osteonecrosis of the jaws, Bisphosphonate related osteonecrosis of the jaw, BP osteonecrosis, Osteochemonecrosis, Bisphossy jaw.

That given by the American Association of Oral and Maxillofacial Surgeons (AAOMS) is the most widely used; 'Patients may be considered to have [BONJ] if they have exposed bone in the maxillofacial region for at least 8 weeks, are currently on or have taken bisphosphonates and have no history of radiotherapy to the jaws', but clear definitions are not given in all reviews of patients.[15–17] One problem is that in stage 0 BONJ there is no exposed bone, which is contradictory with the basic definition and Colella et al. suggested a modification of the basic definition to read 'exposed or otherwise necrotic bone'.[18] Some patients may also present with severe pain or infection which on inspection is associated with necrotic bone, but where there is no mucosal defect, and it is again not clear how to fit these patients into current staging systems.

Pathophysiology

The pathophysiology of BONJ remains unknown, with a number of theories promoted, and possibly interlinking. Factors which are thought to play a part include the suppression of bone turnover, and soft tissue toxicity, which are compounded by the presence of infection and other drugs or pathologies which suppress bone or soft tissue healing, or the immune response.

BPs are taken up by the skeleton and produce most of their effect on osteoclasts when they resorb bone as part of its normal metabolic turnover. The BP is released into the demineralised matrix within the osteoclast border and absorbed by it.

This background metabolic process is increased in response to trauma, including invasive dental treatment, and infection. The maxillofacial skeleton does not appear to accumulate BP at significantly higher concentrations than the remainder of the skeleton despite its higher turnover.[19] Bisphosphonate drugs have been clearly shown to have a direct toxic effect on the soft tissues of the oral cavity in vitro, an effect which is increased in a low pH environment, such as may be found in the presence of local infection.[20] It is not clear however that BP are found in the tissues at a high enough concentration to produce this toxic effect in vivo, during normal oral or parenteral administration. The uptake of BP by the skeleton is so efficient that concentrations in human plasma are un-measurable within a short period of BP administration, and there is no evidence that BP released from bone during its metabolism, even in the presence of increased resorption associated with low pH, reaches concentrations sufficient to be toxic.[1] (*Public assessment reports; Alendronic acid. PL20075/0070-1 UK/H/1156/02-03/DC. Pamidronate disodium. UK/H/1869/001-3/DC PL30306/127-9. Available at* www.mhra.gov.uk).

There may be some reduction in vascularity of bone affected by BP as a result of their anti-angiogenic properties but this is not particularly supported by histological studies which show normal vasculature.[6] It therefore seems unlikely that reduced vascularity plays an important role in the initiation of BONJ, although in progressing lesions local areas of bone will become devitalised and subsequently sequestrate.

The question has often arisen as to why osteonecrosis related to bisphosphonates only arises in the maxillofacial skeleton. The answer is thought to be related to the relatively high turnover of alveolar bone, and to the exposure of the maxillofacial skeleton to the outside environment through the teeth and periodontal ligament.

Clinical presentation, and staging of BONJ

Patients may present during routine dental assessments as having asymptomatic exposed alveolar bone, without any evidence of erythema or discharge or present with pain and evidence of local infection, or occasionally widespread infection, a discharging sinus or even a pathological fracture of the jaw. There may be a history of invasive dental treatment or local trauma from dental prosthesis but in some cases there will be no obvious preceding factor.

Staging of a disease allows for grouping of similar patients to compare outcomes and results of treatments, and the same holds true for BONJ where several different staging systems have been proposed, but the simple clinically-based staging system proposed by Ruggiero et al has been the most widely accepted and used in most publications and guidelines on BONJ (Figs. 1–3).[21] This was revised in the AAOMS position paper in 2009 (Table 2).[17]

Novartis used a staging system based on the National Cancer Institute Common Toxicity Criteria, but this is not been widely adopted.[22]

McMahon et al proposed a different classification system which took into account early and intermediate findings from clinical imaging and biopsy material.[23] They argued that their staging system more clearly identifies patients with early disease allowing decisions to be made about continuing BP therapy and undertaking treatment, but there is little evidence that this improves outcomes. Kwon et al used the serum C-terminal cross-linking telopeptide of type 1 collagen (CTX) into an osteonecrosis scoring system in an attempt to more accurately stage patients on the basis of outcomes.[24]

Incidence of BONJ

Establishing the incidence of BONJ remains difficult, in part because of differences in definitions used for the condition, but it is also likely that some mild, self-resolving cases are not identified.

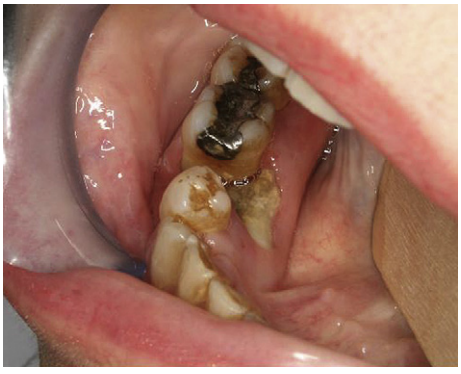

Fig. 1 – Stage 1 BONJ of the mandible.

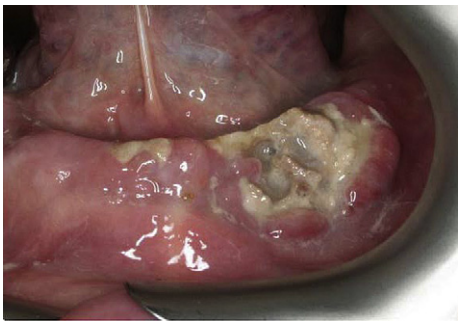

Fig. 2 – Stage 2 BONJ of the mandible.

The incidence of BONJ associated with parenteral administration has been easier to establish as these are generally administered in patients with cancer who are otherwise under close observation, and because the condition appears to develop after less time than with orally administered BP. Frequency rates ranging from 0.94% to 10% in different population groups with differing drug regimes have been published.[25,26]

The incidence in patients administered oral BP, predominantly for osteopenia, are less clear as they are generally prescribed in the community with no specific patient follow-up, and the time to development of BONJ may be 10 or more years. Published figures have ranged from 0.7 per 100,000 prescribed patient years to 0.34% in patients who have undergone dental surgery.[27,28] Whilst this is clearly an uncommon complication of oral BP administration, the sheer volume of prescriptions of BP worldwide means that many cases will present.

Only the establishment of large scale population registries of patients prescribed BP with long term follow-up is likely to provide definitive answers on the incidence of BONJ because of the aforementioned difficulties and the difficulties in separating out the many associated co-morbidities. In the UK all cases of BONJ should be reported to the medicines and healthcare regulatory authority (MHRA) which collates information related to all adverse drug events. Cases reported to the MHRA as of October 2010 are presented in Table 3.

In 2008 a national audit was designed in the UK to try and estimate national incidence, and examine the effect of BP prescribed and duration, to collect data on co-morbidities and risk factors and to collect 12 months treatment and outcome data. The intention is to collect data on new cases from 1st June 2009 to 31st May 2011. Data can be entered in paper or online format (www.rcseng.ac.uk/bijn-project).

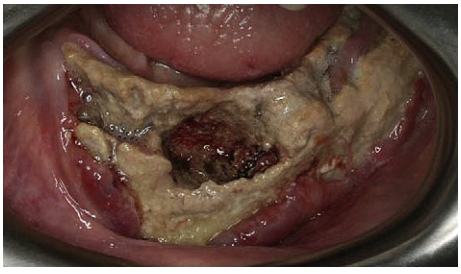

Fig. 3 – Stage 3 BONJ of the mandible.

Table 2 – Staging of Bisphosphonate Related Osteonecrosis of the Jaws. Based on recommendations of the American Association of Oral & Maxillofacial Surgeons.[14]

Stage	Clinical features
Stage 0	No apparent exposed/necrotic bone (but who present with signs and/or symptoms suggestive of future disease)
Stage 1	Exposed/Necrotic bone in asymptomatic patient with no evidence on infection
Stage 2	Exposed/Necrotic bone associated with localised infection
Stage 3	Exposed/Necrotic bone associated with pathological fracture, extra-oral fistula or extension in to surrounding basal bone

Management

The aims of treating patients with BONJ are to eliminate clinical symptoms such as pain, treat any infection of the soft tissues or bone, and minimise the progression of bone necrosis.[15] Clinical markers of success include an intact mucosa with no signs of infection or sinus formation and radiographic markers include the arrest of progression of the bony abnormality or remodelling of the affected area.[29] It is not expected that treatment will lead to resolution of all mucosal lesions, but exposed bone per se is not automatically a problem.[30–32]

Non-surgical management

The use of antiseptic mouthwashes (chlorhexidine gluconate or hydrogen peroxide) and/or analgesia is proposed for patients with clinical evidence of BONJ (such as exposed bone) but in the absence of any evidence of infection (AAOMS Stage 1).[15,17] It is essentially a strategy to reduce the likelihood of further progression of BONJ and avoid infection of exposed bone.[30]

Table 3 – Adverse drug reactions reported to the MHRA, up to October 2010. Bone osteonecrosis given as total number of cases of osteonecrosis reported (number of cases of osteonecrosis of the jaw specifically reported).

Drug (all preparations)	Oral Pain	Mouth Ulceration	Jaw Pain	Bone Osteonecrosis (Jaw)
Alendronic Acid	10	50	8	59 (36)
Clodronic Acid	0	0	0	12 (0)
Etidronic Acid	2	5	0	0 (0)
Ibandronic Acid	1	4	5	29 (18)
Risedronic Acid	2	4	4	12 (8)
Pamidronic Acid	2	0	5	40 (27)
Zoledronic Acid	12	7	30	184 (90)

Where there is evidence of local inflammation or infection, antibiotics are advised.[15,32] Broad spectrum antimicrobial therapy (phenoxymethylpenicillin, amoxicillin or co-amoxiclav or clindamycin ± metronidazole) is recommended although the correct duration of treatment is not clear.[15,32–34] This approach is indicated for patients with what is generally categorised as stage 2 BONJ, but it may also be the preferred approach in patients with BONJ and cancer with very poor prognosis in whom more extensive treatment is not indicated.[15,17,34]

Surgical management

The goal of surgical treatment is to remove necrotic bone and create soft tissue coverage of remaining healthy bone. The difficulty with this approach is knowing how much bone removal is sufficient because as BP are administered systemically and affect the whole bony skeleton, there is effectively no unaffected bone.[15,35,36]

The most commonly recommended approach is to remove symptomatic bony sequestra with minimal soft tissue disturbance and avoiding further bone exposure, although some authors advocate more extensive soft and hard tissue debridement and primary closure of the wound.[15,37]

More radical surgical management is advocated where there are large segments of necrotic bone or where there is pathological fracture of the bone (AAOMS stage 3).[15,17]

En bloc resection of alveolar and basal bone of the maxilla and mandible can then be reconstructed with a combination of local or regional flaps or vascularised or non-vascularised free flaps. In the maxilla an oral–nasal or oral–antral communication may be managed with an obturator.[17,38,39]

Adjunctive therapies suggested for the management of BONJ include hyperbaric oxygen (HBO), parathyroid hormone, platelet rich plasma and lasers. With the exception of HBO, the literature consists primarily of small case series and further studies need to be undertaken before any are considered for routine use.[15]

Prevention of BONJ

The difficulties in treating BONJ highlight the need for preventive measures to avoid its development in the first place. A particular problem is that many patients are forgetful about receiving BP therapy due to the fact that some of these preparations are prescribed on a weekly basis, or may be prescribed within the secondary care setting and therefore not be evident on repeat prescriptions from their General Medical Practitioner.[40]

There is some consensus for the need for patients being dentally fit prior to commencement of intravenous BP therapy, and evidence is emerging that careful dental preparation of patients prior to BP therapy reduces their risk of BONJ.[35,41,42]

When a patient presents to a dental care professional prior to the commencement of BP they should undergo a full assessment of the dental hard and soft tissues, including examination of any dental prosthesis.[35,43] The condition of the teeth should be considered in the context of the patient's general health, as it may be more prudent to extract at an early stage teeth that are unlikely to survive the patients lifetime, but conversely in patients of poor survival prognosis a more pragmatic view should be taken.[34]

Oral hygiene instruction should be included as part of the dental review to minimise the risk of future dental pathology.[35] Furthermore, patients should be instructed in the clinical signs and symptoms of BONJ and advised to seek professional advice early if concerned.[17]

When dental problems are identified in patients prior to commencing BP therapy, every effort should be made to undertake any necessary treatment, particularly extractions, before the drug treatment starts.

As BONJ is predominantly associated with long term use of BP (for oral BP most cases have been administered for at least 3 years, whereas for parenteral administration cases are commonly described after 12 months), dental treatment should not automatically delay the commencement of BP treatment.[15,17,34]

Dental treatment planning

BONJ is most commonly associated with procedures that stimulate the alveolar bone, and therefore is particularly associated with dental extractions, implantology and periodontal surgery, although non-interventional causes of bone stimulation such as periapical or periodontal infection may have the same effect.[35]

High risk procedures be avoided, with reliance on restorative treatment including root canal treatment and non-surgical periodontal treatment.[17,43,44]

The use of osseointegrated dental implants is subject to some controversy. Although some have reported good success rates for implants in patients on BP, the nature and duration of the BP prescription are generally not clearly defined, and it would be expected that the risk of implant complication is low in patients on low potency BP for short periods.[15,45] The patient specific risks should therefore be considered when contemplating implant treatment, and patients appropriately consented.

It is unrealistic to suggest that dento-alveolar surgery must be avoided in higher risk patient groups, as this is dictated by the clinical need of the patient, but consideration should be made for less invasive procedures and where invasive treatment is required, the patient appropriately consented.

There has been much discussion as to the benefits of stopping the drug for a period, a so called 'drug holiday'. It is suggested that cessation of BP treatment allows for regeneration of osteoclasts and therefore improved bone turnover, and this has some support from studies looking at biochemical markers of bone turnover, but there is no consensus on the duration of drug holiday necessary.[17,35] Any decision on temporary cessation of BP therapy must obviously be taken in conjunction with the prescribing physician and whether this is possible will be determined by the clinical indication for BP therapy.

The use of biochemical markers of bone turnover to assess the risk of BONJ in those requiring invasive dental treatment has been suggested and although an attractive idea, results showing an improvement in outcome over other best practice are as yet absent.[46,47]

Prophylactic treatments

Measures proposed to reduce the risk of BONJ where invasive dental treatment is necessary in patients already taking BP include the use of peri-operative antibiotics and chlorhexidine mouthwash, although there is little evidence currently showing benefits in their use.[48–50]

Conclusions

Bisphosphonate osteonecrosis of the jaws is an uncommon, but potentially very serious adverse consequence of BP drug therapy. It is mostly associated with the use of more potent amino-bisphosphonates for extended periods of time.

The most common preceding event to the development of clinical lesions is invasive dental treatment, and it is therefore particularly important that dental health professionals have an understanding of its causes and management.

Prevention remains the most important aspect of management and commences at the time of first prescription, and must continue for the remainder of the patient's life because of the long lasting effect of these drugs on bone.

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