



Bisphosphonates-Related Osteonecrosis of the Jaw – Hospital Sultanah Aminah, Johor Bahru Experience

Chai MB¹, Hock LK², Yahya AF³

¹ Consultant Oral Surgeon, Department of Oral Surgery, Hospital Sultanah Aminah, Johor Bahru

² Dental Officer, Department of Oral Surgery, Hospital Sultanah Aminah, Johor Bahru

³ Dental Officer, Department of Oral Surgery, Hospital Sultanah Aminah, Johor Bahru

ABSTRACT

The increasing use of bisphosphonates in the treatment of bone condition such as osteoporosis and metastatic cancer has led to the increasing number of cases of bisphosphonate-related osteonecrosis of the jaw. The aim of this article is to highlight a case of bisphosphonate-related osteonecrosis of the jaw that developed after dental extraction. This patient had been taking oral bisphosphonate for the treatment of osteoporosis, a side effect of long-term steroid treatment for her rheumatoid arthritis. All dentists should be aware of this serious complication when treating patients who are taking bisphosphonates.

Key Words: Bisphosphonate, Osteonecrosis

Please cite this article as: Chai MB, Hock LK, Yahya AF. Bisphosphonates-Related Osteonecrosis of the Jaw – Hospital Sultanah Aminah, Johor Bahru Experience. Malaysian Dental Journal 2012; 34(1): 13-16.

INTRODUCTION

Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is defined as an area of exposed bone within the maxillofacial region that has persisted for more than 8 weeks after identification by healthcare worker, or had been exposed to bisphosphonate but had no history of radiation therapy to the craniomaxillofacial region.¹ Marx reported the first cases of BRONJ in year 2003.

Since then awareness on the association of bisphosphonates and osteonecrosis has increased. This had led to the introduction of guidelines on how to provide safe dental treatment to patients on bisphosphonates in the year 2006. BRONJ may occur after traumatic treatment to the alveolar bone such as dental extraction or it may also occur spontaneously. The lesion may increase in size regardless of the treatment provided, and this eventually leads to poor quality of life.²

Bisphosphonates had been used in the medical field since 1990's although it was actually developed in the 19th century. This group of drug is mainly used in the treatment of osteoporosis, hypercalcaemia, bone malignancies, multiple myeloma, Paget's disease and osteogenesis

imperfecta. Bisphosphonates are available in two forms; oral (eg. alendronate, risedronate, ibandronate, etidronate, tiludronate, clodronate) and intravenous (pamidronate, zoledronate, ibandronate). Bisphosphonates are classified into 3 main groups³:

1. Non-nitrogen bisphosphonate (clodronate, tiludronate, etidronate)
2. Alkyl-amino bisphosphonate (pamidronate, alendronate, ibandronate)
3. Heterocyclic nitrogen bisphosphonate (risedronate, zoledronate)

The second and third groups contain nitrogen, therefore are more bone selective compared to the first group. This case report highlights the oral complication of bisphosphonate and preventions of BRONJ while managing patient who are taking bisphosphonate for treatment of bone condition.

CASE REPORT

Patient was a 66-year old Chinese woman referred to us by a private practitioner for management of painful non-healing socket of tooth 42 and 43. Patient had extraction of both retained roots of 42 and 43 done three days before attending our clinic.

Medical history revealed that she was a known case of rheumatoid arthritis and was on the following medications; Alendronate 70mg weekly, Methotrexate 0.625mg daily and Prednisolone 2.5mg daily. Patient has been taking Alendronate for the past one year.

Clinical examination showed an area of exposed necrotic bone at the site of extraction and ulcerations on the labial mucosa of lower lip. No pus discharge noted. She was treated with Tetracycline 250mg four times daily and three times daily at home irrigation with 0.2% Chlorhexidine mouthwash for two weeks. Patient was reviewed weekly and sharp bone edges were trimmed and smoothed to prevent trauma to the surrounding soft tissues. Subsequent follow-up showed no sign of improvement but worsening of the condition, as the necrotic area extended more posteriorly onto the 44 as well as anteriorly onto 41 areas causing mobility and eventually exfoliation of 41. We only managed to review her for 3 months before she succumbed to pneumonia and sepsis. Since the extraction socket did not heal after more than 8 weeks and patient was on bisphosphonate, she was diagnosed as having BRONJ.



Figure 1. Initial clinical presentation

DISCUSSION

Bisphosphonate-related osteonecrosis of the jaw (BRONJ) has been reported to be an uncommon condition. Incidence of BRONJ is related to the condition in which bisphosphonates are used to treat. It was reported that the incidence of BRONJ in osteoporosis patient treated with bisphosphonates ranged from 0.001%-0.01%.^{4,12} Although the incidence is very low, the case we

reported was associated with the use of bisphosphonate in the treatment of osteoporosis.



Figure 2. Clinical presentation at 3-month review

On the other hand, the incidence of BRONJ increased by about 1000-fold when bisphosphonates are used to treat malignancy.^{1,4,12} BRONJ usually presented with an area of exposed bone, swelling of surrounding soft tissue, ulcerations, loosening of teeth and sometimes with purulent discharge. Patient may also complain of pain over the exposed area and surrounding soft tissue.^{5,10,11} Not all patients on bisphosphonates will develop BRONJ. Multiple risk factors are associated with BRONJ. Relative systemic effective dose has been reported to be one of the main factors. This is dependent on the potency of the drug, dose frequency, amount administered and its bioavailability.⁶ Intravenous forms are generally more potent than the oral forms. There are three proposed properties, which may affect the potency of bisphosphonates. A combination of these three properties will bring about a net potency of the drug.⁴

1. Kinetic binding to bone
2. Zeta potential
3. Enzyme inhibition

Drugs with higher kinetic binding energy such as Zoledronate and Pamidronate will be more potent.⁴ Zeta potential is electrokinetic potential in colloidal systems, in which charges are conferred to the hydroxyapatite of the bone when bisphosphonates bind on it. More positively charged bisphosphonates such as Alendronate and Ibandronate, will cause more bisphosphonates to bind to the bone.⁴ In order for osteoclast to survive and remain active, protein prenylation is vital. Bisphosphonates act as an inhibitor to the farnesyl

pyrophosphate synthase, a key enzyme in protein prenylation.⁴ Oral bisphosphonates are poorly absorbed therefore reduced bioavailability making it less potent compared to its intravenous form.⁶ As bisphosphonates are excreted via the kidney, it should be cautious in patient with renal failure as it may increase the bioavailability of the drug as well. Concurrent use of H2-receptor blocker such as ranitidine may cause an increase in the bioavailability of the bisphosphonates.⁷ Local anatomy may affect the incidence of BONJ. More cases have been reported to occur in the mandible than in the maxilla. The mandible is at least twice at risk compared to maxilla.^{1,6,8} This may also be due to the lack of blood supply in the mandible as compared to the maxilla.⁵

Patients who are on IV bisphosphonate undergoing dentoalveolar surgery are at higher risk of developing BRONJ.¹ The American Association of Oral and Maxillofacial Surgeons had reported an increased risk of as much as 7 times. The risk of developing BRONJ is even higher in cases with existing inflammatory dental diseases such as periodontal or dental abscess.¹ Kyrgidis et al in year 2009 had reported that bisphosphonates may also cause fibroblasts and keratinocytes fail to migrate and multiply leading to defective mucosal wound healing.⁹ Other conditions that dampen the normal healing process such as smoking, diabetes mellitus, prolonged use of corticosteroids, malnutrition, advanced age, AIDS and alcohol abuse may also increase the risk of BRONJ.^{1,5} The patient in our case report was on prolonged prednisolone treatment for her rheumatoid arthritis and that would have lead to slower healing capacity.

As BONJ can be very devastating to the patients and severely affect their quality of life, numerous ways of prevention had been suggested. Before patients are started on bisphosphonates, the prescribing physician should refer them for a thorough dental examination. Any active dental disease should be treated early to avoid later extraction. Dento-alveolar surgery if indicated should be carried out prior to commencement of the drug. Once patient is started on the drug, they should attend regular dental check up.^{1,4,5,6,8} Antibiotic prophylaxis has been advocated for patient undergoing unavoidable dento-alveolar surgery and would be of benefit especially to those receiving IV bisphosphonates. Although antibiotic

prophylaxis for prevention of BRONJ is very much debatable, a survey in 2009 by the British Association of Oral and Maxillofacial Surgeons showed that almost all the consultants would prescribe antibiotics for molar extraction.¹³ The recommended antibiotic is Penicillin V. In cases of allergic to penicillin, doxycycline or metronidazole has been advocated.¹ Drug holiday, which is stopping the drug for 3 months prior to and 3 months after elective oral surgery procedure has also been reported to be effective.¹ After discontinuation of bisphosphonates, the sequestered drug will slowly leach out from the bone. The rate of leaching is dependent on the bone turnover rate. Maxilla and mandible have high bone turnover, therefore, more than 90% of the drug would have been eliminated from the bone after cessation of the drug.⁷

Bisphosphonates should only be stopped if patient's systemic condition allows and after discussion with the prescribing physician and patient. No absolute treatment is available for BRONJ at the moment. Marx et al in 2005 recommended the use of Penicillin V 500mg QID for long term as a mode of treatment for BRONJ.⁸ This can be used together with 0.2% Chlorhexidine mouthwash by patient twice a day for a month. Professional's irrigation is carried out every 72 hours for a month.^{5,14} Some clinicians had also proposed the use of 2% potassium iodine solution together with chlorhexidine mouthwash.¹⁵ If the area of osteonecrosis is large, surgery may be performed. Carlson and Basile in 2009 had reported better surgical outcome in patient taking oral bisphosphonate compared to IV and resection of maxilla showed better healing than mandible.¹⁵ Marginal resection, segmental resection or radical resection with osteocutaneous flap can be carried out depending on case.^{4,16,17}

CONCLUSION

In recent years, we have seen an increase in the number of patients being prescribed with bisphosphonates. Prescribing medical colleagues should always inform the patients of the risk of osteonecrosis of jaw and refer them for a thorough dental examination prior to commencement of the drug. Once the drug is commenced, patients should attend regular maintenance dental check-up.

Prevention is still the best way, as no absolute treatment is available for BONJ till date.

ACKNOWLEDGEMENT

We would like to extend our thanks to the Director General of Health Malaysia and Principal Director of Oral Health Division, Ministry of Health Malaysia for giving us permission to publish this journal.

REFERENCE

1. American Association of Oral and Maxillofacial Surgeons. Position Paper on Bisphosphonate-Related Osteonecrosis of the Jaws. *J Oral Maxillofac Surg* 2007;65:369-76.
2. Migliorati CA. Bisphosphonates and Oral Cavity Avascular Bone Necrosis. *J. Clin Oncol* 2003;21:4253-4.
3. Russell RGG, Watts NB, Ebetino FH, Rogers MJ. Mechanisms of action of bisphosphonates: similarities and differences and their potential influence in clinical efficiency. *Osteoporosis Int* 2008;19:733-59.
4. Arrain Y, Masud T. Bisphosphonates and osteonecrosis of the jaw- Current Thoughts. *Dent Update* 2009;36:415-9.
5. Ruggiero S, Gralow J, Marx R E, Hoff A O, Schubert M M,. Practical guidelines for the prevention, diagnosis, and treatment of osteonecrosis of the jaw in patients with cancer. *J Onc Prac* 2006;2:7-14.
6. Brock G, Barker K, Butterworth C J, Rogers S. Practical Considerations for Treatment of Patient taking Bisphosphonate Medications: An Update. *Dent Update* 2011;38:313-26.
7. Zairowski J. Comment on the American Association of Oral and Maxillofacial Surgeons statement on bisphosphonates. *J Oral Maxillofac Surg* 2007;65:1440-1.
8. Marx RE, Sawatari Y, Fortin M, Broumand V. Bisphosphonate-induced exposed bone (osteonecrosis/osteopetrosis) of the jaws: risk factors, recognition, prevention, and treatment. *J Oral Maxillofac Surg* 2005;63:1567-75.
9. Kyrgidis A, Vaihtsevanos K. Risk factors for bisphosphonate-related osteonecrosis of the jaws. *J Oral Maxillofac Surg* 2009;67:2553-4.
10. American Dental Association Council on Scientific Affairs. Dental management of patients receiving oral bisphosphonate therapy: Expert panel recommendations. *J Am Dent Assoc* 2006;137:1144-50.
11. Hewitt C, Farah C S. Bisphosphonate-related osteonecrosis of the jaws: a comprehensive review. *J Oral Pathol Med* 2007;36:319-28.
12. Khosla S, Burr D, Cauley J, Dempster D, Ebeling P, Felsenburg D et al. Bisphosphonate-associated osteonecrosis of the jaw: Report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res* 2007;22:1479-91.
13. Rogers SN, Hung J, Barber AJ, Lowe D. A survey of consultant members of the British Association of Oral and Maxillofacial Surgeons regarding bisphosphonate-induced osteonecrosis of the jaws. *Br J Oral Maxillofac Surg* 2009;47:598-601.
14. Bagan J, Blade J, Cozar J M, Constela M. Recommendations for the prevention, diagnosis, and treatment of osteonecrosis of the jaw (ONJ) in cancer patients treated with bisphosphonates. *Med Oral Patol Oral Cir Bucal* 2007;12:E332-40.
15. Pires FR, Miranda A, Cardoso ES et al. Oral avascular bone necrosis associated with chemotherapy and bisphosphonate therapy. *Oral Dis.* 2005;11:365-9.
16. Carlson ER, Basile JD. The role of surgical resection in the management of bisphosphonate-related osteonecrosis of the jaws. *J Oral Maxillofac Surg* 2009;67 (5 Suppl):85-95.
17. Mucke T, Haarmann S, Klaus-Dietrich W, Holzle F. Bisphosphonate related osteonecrosis of the jaws treated by surgical resection and immediate osseous microvascular reconstruction. *J Craniomaxillofac Surg* 2009;37:291-7.

Corresponding Author:

Dr Daniel Lim Khim Hock
Department of Oral Surgery
Hospital Sultanah Aminah
Jalan Abu Bakar, 81100 Johor Bahru
Email: daniel_khlim@hotmail.com