“A REVIEW OF BISPHOSPHONATES—POSSIBLE MODES OF ACTION, ALTERNATIVE DRUGS AND IMPLICATIONS FOR DENTAL IMPLANT TREATMENT”

Dr Elliott Ballantyne B.A. Mod (Physiology), B.A., BDentSc (TCD), MFD RCSi, MSc (Dental Implantology)

University of Bristol and The Dental Implant Clinic, Bath, UK.

Introduction
- Bisphosphonates are used over 40 years to treat variety of diseases
- Osteoporosis
- Paget’s disease
- Hyperparathyroidism of malignancy
- Osteolytic lesions of multiple myeloma
- Bone metastases associated with breast, prostate, lung and other soft-tissue tumours

Prevalence
- Top 100 most prescribed medicines in US (Epstein et al., 2012)
- 30 million prescriptions in US
- 180 million worldwide (Madrid and Sano, 2009)
- IV-bisphosphonates, Zoledronate and Pamidronate, prescribed to over 2.5 million patients worldwide
- Prevalence of osteoporosis – 75 million in US, Europe and Japan (Ghada and Louis, 2007)

Risk Factors associated with osteonecrosis

Systemic Factors
- Age
- Systemic disease (renal failure, anaemia, obesity, diabetes)
- Smoking

Concurrent medication
- Immunomodulators
- Chemotherapeutic agents
- Bisphosphonate related factors

Pharmacy
- Duration of treatment

Local risk factors
- Dental surgery
- Oral infection (periodontal and dental abscesses)
- Poor oral hygiene
- Intratissue

Incidence of Bisphosphonate Related Osteonecrosis of the jaw (BRONJ)

Osteoporosis
- 4.3%

Malignancies
- 0.8-5.5%

Immunosuppressants
- 1.2-11%

Multiple Myeloma
- 3.0-21%

Prostate cancer
- 3.0-10%

Waller et al., (2012)

Bonomi et al., (2011)

0.0-1-0.4% in patients with osteoporosis on oral BP > 10 fold duration

0.0-0.1-15% in patients with cancer on iv-BP > 6-7.0-1% following iv.

Classification of bisphosphonates

Bisphosphonates are classified as:

1. Non-nitrogen containing bisphosphonates (NP)
   - Omeprazole

2. Nitrogen containing bisphosphonates (NP)
   - Alendronate

Cellular mechanism- Non-nitrogen containing bisphosphonates

- Formation of non-hydrolysable (App)PgY orthoester metabolites (Riisamo et al., 2008, 2010).
- Intracellular accumulation of these metabolites within osteoclasts inhibit their function.
- Induction of osteoclastic apoptosis (Coxon et al., 2006).

Classification of bisphosphonates

Bisphosphonates are classified as:

1. Non-nitrogen containing bisphosphonates (NP)
   - Omeprazole

2. Nitrogen containing bisphosphonates (NP)
   - Alendronate

Cellular mechanism- Non-nitrogen containing bisphosphonates

- Formation of non-hydrolysable (App)PgY orthoester metabolites (Riisamo et al., 2008, 2010).
- Intracellular accumulation of these metabolites within osteoclasts inhibit their function.
- Induction of osteoclastic apoptosis (Coxon et al., 2006).

Materials and Methods
- An electronic Medline search was conducted to find relevant articles from both medical and dental literature between 1980 and 31st December 2014 that fulfilled specifically defined inclusion and exclusion criteria. The Cochrane Database of Systematic Review, the Cochrane Central Register of Controlled Trials and Embase were searched for English language studies published between 2000 and 31st December 2014.
- The literature search was compiled by cross checking the references cited in all relevant identified publications to ensure that no articles were missed.
- Type of study:
  - The main difficulty with studies on this topic is obtaining a large enough prospective sample to determine the rate of failure.
  - The statistical requirements for a study to be relevant will need to be explored in a recent study by Goss et al., (2010).
- Results:
  - A total of 37 articles were included in the current review.
  - A total of 8 retrospective studies and 2 case series studies evaluated the success rate of dental implants in patients with a history of bisphosphonate use. The remaining 17 articles consisted of case series and case reports.
  - 2 articles were evaluated from the Cochrane Library that were considered to be relevant in terms of interventions for reasoning osteoncrosis of the jaw bone associated with bisphosphonates.
  - A second search of the Medline and Embase databases, regarding Bisphosphonates (MeSh) in conjunction with the term “oral soft tissues” yielded a total of 12 articles that were included in this review.

Operative protocol for patients receiving oral bisphosphonates

Perioperative oral antibiotics for 7 days, starting 48 hours before surgical intervention.
- Oral antibiotics: Dicloxacilin or amoxicillin and clavulanic acid (875 mg/125 mg) every 12 hours or, in cases of penicillin allergy, clindamycin 600 mg every 8 hours.
- The surgical procedures can be performed under local anaesthesia, sedation or GA.
- After surgery, all bony edges around the region of surgery should be strictly smoothed by use of a surgical bur.
- In cases of tooth extraction
- Full thickness vestibular mucoperiosteal flap
- Release the periosseous for primary closure
- Follow up patients at 1, 2, 4, and 12 weeks and 6 and 12 months postoperatively.
- Perioperative oral antibiotics for 7 days, starting 48 hours before surgical intervention.

Results
- The initial search of Medline and Embase databases, regarding bisphosphonates and dental implants, yielded a total of 37 articles which were considered for the study. On further investigation 27 studies met the study inclusion criteria. 10 articles failed to meet the inclusion criteria and were excluded from the results.
- A total of 8 retrospective studies and 2 case series studies evaluated the success rate of dental implants in patients with a history of bisphosphonate use. The remaining 17 articles consisted of case series and case reports.
- 2 articles were evaluated from the Cochrane Library that were considered to be relevant in terms of interventions for reasoning osteoncrosis of the jaw bone associated with bisphosphonates.
- A second search of the Medline and Embase databases, regarding Bisphosphonates (MeSh) in conjunction with the term “oral soft tissues” yielded a total of 12 articles that were included in this review.

Guidelines for treating your patients on bisphosphonates

Patients on oral bisphosphonates
- Consult with prescribing physician.
- Teeth that cannot be restored: endodontic treatment of the remaining roots should be considered.
- Effective denstal operative surgical procedures, present a unnecessary risk and are contraindicated in patients undergoing treatment with n-bisphosphonates.

Oral Bisphosphonates
- If there is an urgent need for oral surgery while taking oral bisphosphonates, as in the presence of odontogenic abscesses requiring extraction or abscess drainage to decrease pain and to manage infection, the patient should be subjected to the appropriate procedure rather than maintaining the condition of pain and infection.
- It is necessary to inform the patient of possible risks.

Patients receiving oral bisphosphonates less than 3 years
- It is not necessary to change or delay the oral surgical implant/periodontal treatment plan.

Patients receiving oral bisphosphonates less than 3 years with at least one systemic risk factor
- It is necessary to contact the physician to discontinue the bisphosphonate (drug holiday) for at least 3 months before the surgical procedure and the prescription should be delayed until 3 months after.

Patients receiving oral bisphosphonates greater than 3 years
- Osteoporosis and bone turnover disorders (pathological fracture/year/bad)
- Contact the physician to agree an interruption of the drug for 3 months before the surgical occasion.
- There is no evidence to support or disprove the effectiveness of a drug holiday.
- For a standard 70mg dose of Alendronate administered for 7 years, it can take 9 months for bone marrow osteoclasts to become sufficiently active again.

Patients receiving oral bisphosphonates with co-morbid risk factor
- Increased risk of osteonecrosis.
- Consult with prescribing physician.

Other hypotheses

- Interfere with specific metabolic pathways
- Interact with specific metabolic pathways
- Modulate bone turnover and inhibit osteoclast function
- Modulate bone turnover by inhibiting osteoclast function
- Mevalonolactone biosynthetically

Biochemical mechanism-Nitrogen containing bisphosphonates
- Intact with specific metabolic pathways
- Mevalonolactone biosynthetically
- Interact with specific metabolic pathways