

Bisphosphonates and Osteonecrosis of the Jaws

Osteonecrosis

- **Osteonecrosis:** Death of bone cells, bone endothelial cells and vasculature with resulting impairment of blood supply to the bone (also called avascular necrosis or ischemic necrosis)
- Common causes of osteonecrosis include:
 - High-dose radiation therapy (osteoradionecrosis)
 - Osteomyelitis (microbial infection)
 - Avascular necrosis (esp. hip) secondary to the prolonged use of corticosteroids
 - Trauma
 - Thromboembolism

Osteonecrosis of the Jaws

- Recently, the use of bisphosphonates, has been recognized as a cause of a distinct type of osteonecrosis occurring exclusively in the jawbones
- Most cases of ONJ have been reported following the use of IV administration of the drugs, especially Aredia and Zometa, however, it has also been reported following the use of oral medications, such as Fosamax
- It appears that the risk of occurrence of ONJ is much lower with oral medications than with the IV drugs

Case Definition of ONJ (AAOMS 2007)

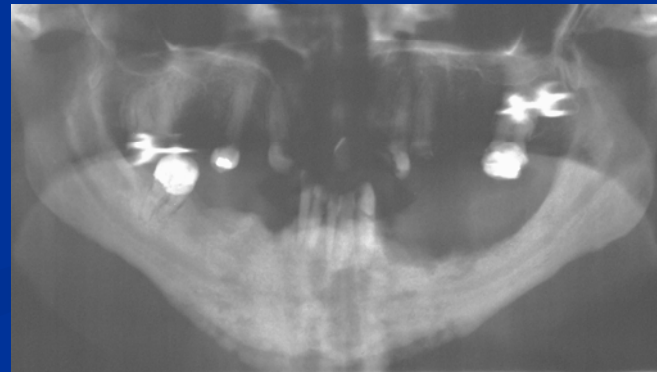
- Current or previous treatment with a bisphosphonate
- Exposed bone in the maxillofacial region that has persisted for more than eight weeks
- No history of radiation therapy to the jaws

Osteonecrosis of the Jaws

Woo, Annals of Internal Med, 2006;144

- Review of 368 reported cases:
 - 94% treated with IV pamidronate (Aredia) or zolendronic acid (Zometa)
 - 85% with multiple myeloma or breast cancer
 - 6% taking oral BPs for osteoporosis or Paget's disease
- The mandible is affected twice as often as the maxilla
 - Mandible 65% (most over mylohyoid ridge)
 - Maxilla 26%
 - Both 9%
- Females over males 3:2

- 60% of cases occurred after tooth extraction or dentoalveolar surgery; 40% occurred spontaneously over bony exostoses or under dentures
- Median duration of drug use at time of diagnosis ranged from 22 to 39 months
- Characterized by tissue dehiscence, chronic bone devitalization, hypocellularity, and lytic radiographic features
- As many as 1/3 of cases may be asymptomatic unless secondarily infected
- Often refractory to usual treatment approaches (hyperbaric oxygen, antibiotics, surgical resection of necrotic bone)



Courtesy of D. Damm, DDS

What are Bisphosphonates?

- Originally synthesized in 1865 and used as inhibitors of corrosion, in fertilizers, and in the oil industry
- They are powerful inhibitors of osteoclastic activity and bone resorption and therefore improve bone mineral density by decreasing bone turnover
- They are used intravenously to treat hypercalcemia associated with various malignancies such as prostate and breast, osteolytic lesions of cancer metastasis and multiple myeloma; injected every 3-4 weeks
- They are also used orally to treat/prevent osteoporosis; taken daily, weekly or monthly
- The IV doses for oncologic indications are often up to 12 times higher than those used for osteoporosis

Pharmacology of the Bisphosphonates

- Low intestinal absorption with only about 5% bioavailability but taken up rapidly by bone; bioavailability via the IV route is much greater
- Remarkably persistent drugs; once in bone, they are released only when the bone is destroyed in the course of normal turnover with skeletal half-lives as long as 10 years (Fosamax)
- Osteoclasts phagocytize the bound BP; the ingested BP causes a reduction in osteoclast activity and eventually death of the osteoclast

Beneficial Effects of BPs

- Prevent and reduce hypercalcemia associated with metastatic bone disease
- Reduce skeletal complications (pathologic fractures, spinal cord compression)
- Anti-tumor effects
 - Induction of tumor cell apoptosis
 - Inhibition of tumor cell adhesion
 - Inhibition of tumor invasion
 - Antiangiogenesis
- Prevent or treat osteoporosis
 - Of those people who break a hip, 20% die within 1 year due to sequelae of the fracture

Adverse Effects of BPs

- GI disturbances with oral formulations
- Adverse skeletal effects with long term use (controversial)
 - Hypodynamic bone with decreased biomechanical competence
 - Oversuppression of bone turnover yielding hard, brittle bone with an increased risk for fracture
 - Retarded healing
 - Slow callus remodelling
- Osteonecrosis of the jaws

Review of ONJ (368 cases)

Woo, Annals of Internal Med, 2006;144

Agent	Reported Cases
Zoledronic acid (Zometa)	124
Pamidronate (Aredia)	110
Pamidronate+Zoledronic acid	100
Alendronate (oral)(Fosamx)	15
Alendronate+ Zoledronic acid	2
Risidronate (oral) (Actonel)	1
Ibandronate (oral) (Boniva)	1
Ibandronate+Zoledronic acid	1
Pamidronate=Zoledronic acid+Alendronate	1

Estimated Incidence of ONJ

- With IV bisphosphonates
 - 0.8% to 12% based on cumulative incidence data
- With oral bisphosphonates
 - It is estimated that up to 30 million prescriptions for BPs are written each year
 - Estimated occurrence of 0.7/100,000 person/years of exposure with Fosamax (Merck)
 - 0.01% to 0.04% spontaneous occurrence (Australian data)
 - 0.09% to 0.34% after extractions (Australian data)
 - 4% - Sedghizadeh, et al, JADA 2009;140;61-66
- Incidence increases with dose and time of exposure
- True incidence is unknown

“Because you are taking a type of drug called a bisphosphonate, you may be at risk for developing osteonecrosis of the jaw and certain dental treatments may increase that risk.”

Possible Risk Factors

- Potency of the bisphosphonate
- Duration of administration (> 3 years for oral)
- Over age of 65
- Chronic oral glucocorticoid use
- Estrogen replacement therapy
- Diabetes
- Smoking
- Periodontal disease; dental abscesses
- Dentoalveolar surgery
- Local anatomy (tori, exostoses, mylohyoid ridge)

Guidelines / Recommendations

- American Dental Association Report of the Council on Scientific Affairs – July 2008
- Ruggiero, S, et al: Practical guidelines for the prevention, diagnosis, and treatment of osteonecrosis of the jaw in patients with cancer. J Oncol Prac 2006; 2(1):7-14
- American Association of Oral and Maxillofacial Surgeons Position Paper 2007
- International Myeloma Foundation 2006

Management Guidelines (ADA 2008)

Oral Bisphosphonates: Prevention

- **Prior to beginning oral BP therapy:**
 - Ideally, patients should have a comprehensive oral evaluation and invasive dental treatment completed prior to starting on BPs
 - Patients should be educated about the risks of BP therapy and the need for good OH and regular dental check-ups

Management Guidelines (ADA 2008)

Oral Bisphosphonates: Prevention

- For patients currently taking oral BPs:
 - Routine dental treatment should not be modified solely on the basis of BP therapy
 - Prior to invasive treatment involving bone or periosteum, patients should be informed of the risk for ONJ and alternative treatment options; risk is felt to be exceedingly small
 - Aggressive treatment of areas of active infection (e.g. PA pathoses, sinus tracts, purulent perio pockets, severe periodontitis, abscesses)
 - For bone/periosteal manipulation, treat one sextant or tooth initially, then wait at least 2 months before continuing; patient should be placed on antimicrobials (chlorhexidene BID) during that period

Special Issues

- **Oral and Maxillofacial Surgery**
 - Discussion of risks
 - AAOMS: ONJ is unlikely if taken oral BPs < 3years (clinical observation)
 - AAOMS: if oral BPs taken > 3 years, consider stopping BPs for 3 months before ext (no data to support this)
 - Marx: if oral BPs taken > 3 years, recommends CTX blood test to determine treatment timing (no peer reviewed data to support this; controversial)
 - Discussion of alternative treatment options (e.g. endo)
 - Conservative technique with primary closure
 - Chlorhexidene mouthrinse BID x 2months
 - Consider using prophylactic antibiotics during healing/wound closure phase (amoxicillin plus metronidazole; clindamycin, or azithromycin)

Special Issues

■ Endodontics

- Endo treatment is preferable over surgical manipulation, if tooth is salvageable; manipulation beyond the apex is not recommended

■ Restorative Dentistry

- All routine restorative procedures can be carried out

Management Guidelines (Ruggiero 2006)

IV Bisphosphonates: Prevention

■ Prior to beginning therapy:

- Ideally, patients should have a comprehensive oral evaluation, including a panoramic film, prior to starting on IV BPs
- If circumstances allow, any procedure that requires bone healing should be completed before IV BP therapy begins (i.e. ext of non-restorable teeth or with a poor prognosis); a decision to defer BP therapy must be made by the oncologist
- Complete and removable partial dentures should be evaluated for their potential to induce soft tissue injury, especially over tori, exostoses, and the mylohyoid ridge, and adjusted if required
- Patients should be educated about the importance of maintaining good OH and regular dental check-ups (~every 3-4 months)

Management Guidelines (Ruggiero 2006)

IV Bisphosphonates: Prevention

- **Currently Receiving IV BP Therapy:**
 - Patients should be educated about the importance of maintaining good oral hygiene and regular dental check-ups
 - Complete and removable partial dentures should be evaluated for their potential to induce soft tissue injury, especially over tori, exostoses, and the mylohyoid ridge, and adjusted if required
 - RCT is preferable over extractions when possible; coronal amputation may be necessary with retention of remaining roots
 - Elective jaw surgery should be avoided
 - Implants not recommended

Prediction of Complications (Suggested by Marx, R.)

- CTX (C-terminal cross-linking polypeptide) blood test
- CTX (breakdown product of collagen) used as a marker of bone remodeling activity
 - The less activity the greater the risk for ONJ
- Test is only available from: Quest Diagnostics, San Juan Capistrano, CA
- **Test has not been independently validated and is controversial**

CTX Value	ONJ Risk
300-600 pg/ml	None
150-299 pg/ml	None or minimal
101-149 pg/ml	Moderate
<100 pg/ml	High

Treatment of ONJ (Ruggiero 2006)

- Referral to an oral and maxillofacial surgeon and oncologist
- Minimal surface bony debridement to reduce sharp or rough bone surfaces
- Biopsy is not indicated unless metastasis is suspected
- Consider fabrication of a protective stent (thin vinyl or thin acrylic) to cover exposed bone, making sure it does not cause further trauma to the osteonecrotic site
- Check dentures for areas causing trauma to soft tissues and adjust them; consider the use of soft liners
- Consider intermittent or continuous antibiotic therapy following culture and sensitivity testing to prevent secondary infection, pain and osteomyelitis (PCN \pm metronidazole plus oral rinses with chlorhexidine)
- Monitor patients at least every 3 months
- If surgery becomes necessary, consider stopping BP therapy in coordination with oncologist
- Hyperbaric oxygen not effective

AAOMS Staging and Treatment (2007)

Staging	Treatment
At risk: history of BP treatment but no signs or symptoms	No treatment indicated Education
Stage I: Exposed bone, asymptomatic, no infection	AB mouthrinse, quarterly F/U, education, med consult
Stage II: Exposed bone, pain, infection with or without purulent drainage	Oral Abs, AB mouthrinse, analgesics, superficial debridement
Stage III: Stage II, plus either fracture, extra-oral fistula, or osteolysis to inferior border	Stage II plus surgical debridement or resection