

## **Bisphosphonate-induced osteonecrosis of the jaws (BIONJ)**

Clinical management issues

“What can go wrong, and how to manage it”

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## **Outline**

- Brief history of BIONJ
- Prevention and treatment of intravenous BIONJ
- Prevention and treatment of oral BIONJ

## **Phossy jaw**

- Chronic exposure to white phosphorus vapour
- Deposition of phosphorus in the jaws
- Toothache and gum swelling
- Dying bone was foul-smelling
- Jaws would rot away and glow greenish-white in the dark

## **Consequences of phossy jaw**

- Surgery to the affected jaw might save the sufferers' life
- Otherwise, death from organ failure would follow
- Suicide was common
- Public revulsion forced changes in match manufacture which eliminated the disease

## **Brief history of BIONJ**

- First reported by Marx (Sept '03), though met with scepticism, particularly by some drug manufacturers

## **Increasing awareness**

- JADA Dec 2004 issue - 3 separate publications
- By May 2007, > 300 publications linked bisphosphonates (BPNs) to osteonecrosis in the jaws; approx. 10,000 individual cases were reported
- Most specialties of dentistry have guidelines or position papers, and several medical societies:
  - Mayo Clinic
  - American Society for Bone and Mineral Research
  - American Society of Endocrinology, etc

## Incidence

- True incidence unknown - probably never will be
- In early trials, no oral examination was done – report forms did not list jaw osteonecrosis as a side effect
- Estimated incidence of:
  - IV BIONJ is 0.8-30%
  - oral BIONJ is 0.007-0.01%
- Median is most likely accurate:
  - IV BPNs - 8%
  - oral BPNs - 0.015%
- Sales estimate:
  - 3 million individuals worldwide have received or are receiving IV BPNs
  - 13 million women in the USA alone (many millions more in Europe) are currently receiving BPNs

## Guidelines/statements

### Dental Associations:

- AAOM, Dec 2005
- AAE, 2006
- ADA, 2006
- AAOMS, Sept 2006
  
- Canadian Consensus Practice Guidelines for Bisphosphonate Associated Osteonecrosis of the Jaw, June 2008

## What is BIONJ?

“exposed bone in the maxilla or mandible that fails to heal within 8 weeks in a patient receiving/has received a systemic BPN and who has not received local radiation therapy to the jaws” \*

\* AAOMS. Position paper on bisphosphonate-related osteonecrosis of the jaws. J Oral Maxillofac Surg 2007;65(3): 369-76

## Staging

### Stage 1

exposed bone that is asymptomatic with no evidence of significant soft tissue infection

## Staging

### Stage 2

exposed bone associated with pain, soft tissue and/or bone infection

## Staging

### Stage 3

- pathological fracture
- exposed bone associated with soft tissue infection or pain that is not manageable with antibiotics due to the large volume of necrotic bone

## Evidence-based aspects of ONJ

... there are no guidelines that are strictly evidence-based ...

... the clinical management of the oral complication is largely based on expert opinion ...

American Academy of Oral Medicine position paper, 2005

## Risk factors for BIONJ

- Concomitant use of oestrogen
- Older age (over 65 years)
- Prolonged use of BPNs

American Dental Association guidelines, 2006

- Corticosteroid therapy
- Diabetes
- Smoking
- Alcohol use
- Poor oral hygiene
- Chemotherapy drugs

American Association of OMFS Position Paper, 2006

## Relative risk of BIONJ

- IV
  - An estimated six doses (monthly) of IV BPNs place a patient at risk for BIONJ
- Oral
  - 156 continuous weekly doses (3 yrs) is thought to place patients taking oral Fosamax or Actonel at risk of BIONJ
    - However, no direct causal link has been established between oral BPNs and BIONJ

## Why the difference?

- low lipid solubility of oral BPNs - limits absorption in small intestine to < 1%
- oral BPNs accumulate in bone slowly
- clinically exposed bone tends not to appear until after a 3-year exposure to oral BPNs
- incidence & severity of BIONJ is thought to increase with additional yrs of oral drug use
  - but no evidence for this exists

## Where does BIONJ start?

- Typically in alveolar bone, and extends to:
  - inferior border or rami of the mandible
  - into the zygoma or maxillary sinus walls about the maxilla

## Why does BIONJ start in alveolar bone?

Due to:

1. high bone turnover rate and
2. greater reliance on osteoclast-mediated remodeling in the alveolar bone

Results from occlusal or denture wearing forces on alveolar bone

## What can cause BIONJ?

- periodontal disease
- failing root canal fillings
- abscess formation
- trauma (surgical or other, e.g. denture pressure)

*all increase rate of bone turnover in alveolar bone*

## Clinical signs

- deep bone pain about teeth
- tooth mobility unexplained by dental or other pathology

Not necessarily diagnostic! BPN use is a warning sign

## Location

- Mandible: maxilla = 2:1
- exposed bone may be extensive or relatively small - some cases present as pinpoint exposure with extensive necrotic bone beneath

## Radiographic signs I

- widened periodontal ligament space
- sclerosis of the lamina dura

Neither of which are diagnostic!

## Radiographic signs II

- diffuse, ill-defined radiolucency/opacity

## General symptoms/signs

- exposed bone (necrotic bone beneath)
- dead bone painful when colonised by micro-organisms or infection develops
- micro-organisms usually Actinomyces, Veillonella, Eikenella, and Moraxella sp; all sensitive to penicillin

## Initiating events for BIONJ

	Incidence (%)
Tooth extraction	38
Active periodontitis	29
Spontaneous	25
Perio surgery	4
Dental implant	3
Surgical endo	1

Controlling conditions before BPN therapy helps avoid up to 75% of cases

## Intravenous BIONJ

Used to treat cancer-related bone lesions and hypercalcemia, and osteopenia in prostate cancer patients undergoing androgen-deprivation therapy

## Prevention *before* IV BPNs

- Metastatic tumour deposits in bone are recognised early and proliferate slowly
- 4-6 doses of IV BPN (given monthly) needed to affect bone healing in the jaws
- This gives sufficient time to prepare the oral cavity
- Smoking cessation and alcohol limitation advised

## Prevention *before* IV BPNs

- Eliminate dental pathology ASAP - avoids invasive procedures later
- Remove teeth of doubtful prognosis:- non-restorable, abscessed, with failing root canal fillings, or periodontally compromised
- Perio care - arrest inflammation, salvage treatable teeth, and hygiene education regarding self-maintenance
- Next, restorative and prosthodontic procedures
- New dental implants and adult ortho are not recommended

## Prevention *during* IV BPNs

- Bone healing is unpredictable and risky for BIONJ, thus:
  - avoid invasive oral surgical procedures, (e.g. extractions, implants, perio surgery, ridge augmentation, endo surgery)
- Restorative procedures are safe (crowns, bridges, removable partial and complete dentures)

## Prevention *during* IV BPNs

- treat non-restorable teeth with root canal fillings and crown amputation to avoid extraction
- mobile teeth best splinted if practical
- failing root canal fillings re-instrumented and refilled to avoid extraction, or endo surgery
- if extraction is unavoidable, inform patient of risks of BIONJ and sign consent form

## Managing established IV-BIONJ

- Reinforce that the IV BPN was critical to contain metastatic cancer
- Advise that self-maintenance will reduce possibility of second or third sites developing
- Plan follow-up visits (every 4 months) - must comply with meds
- Exposed bone is likely permanent - requires ongoing monitoring and medications for control
- In some cases, bone resection may be necessary

## Antimicrobials for established IV-BIONJ

- exposed bone without pain
  - 0.12% chlorhexidine 30-mL three times daily
- pain and infection present
  - 0.12% chlorhexidine + penicillin VK 500 mg, QID - OK for long-term use (years) without "super infections" or development of candidiasis
  - if patient concerned about long-term antibiotic use, can be used only during episodes of pain

## Antimicrobials for established IV-BIONJ

- if penicillin allergic:
  - Levofloxacin, 500 mg, once daily - max 21 days
  - Doxycycline, 100 mg, once daily
  - Zithromycin, 250 mg, once daily - max 21 days
- clindamycin not recommended - poor spectrum of activity
- metronidazole (Flagyl), 500 mg, TID for 10-days - aids control of Gram negative anaerobes

## Outcome of IV-BIONJ

- most patients (~90%) achieve a functional and pain-free state with conservative management
- only 5% are non-responsive or progress to a pathological fracture - might require a partial jaw resection
- 5% succumb to the cancer

## Hyperbaric oxygen?

... HBO plus antibiotic therapy is effective in early stage of ONJ ...

(single case report)

Shimura K, Shimazaki C, Taniguchi K, *et al.* Int J Hematol. 2006 Nov;84(4):343-5

... hyperbaric oxygen has not been shown to be effective and, therefore, is not recommended ...

Novartis Expert Panel Recommendation, 2005

## Oral-BIONJ

- less extensive, more responsive to surgery
- limited absorption of BPNs orally extends the minimal risk period to the first 3 years of continuous use
- Fosamax (Alendronate) has more reported cases to date than Actonel (Risedronate)
- In the US, the risk of development has been assessed by a CTX blood test

## CTX test

- fasting serum C-terminal telopeptide (CTX) assay
- measures octapeptide fragment released from type I bone collagen when an osteoclast resorbs bone
- an index of bone turnover:
  - < 100 pg/mL - high risk for BIONJ (suppressed bone turnover and a reduced healing capacity)
  - 100 pg/mL - 150 pg/mL - moderate risk
  - > 150 pg/mL - minimal or no risk
- normal values reported by laboratories performing the test were derived before BPNs and are inaccurate (too wide a range of normal)

## No CTX in Canada?

### Deoxypyridinium (D-Pyd)

- 90% of organic matrix of bone is Type I collagen
- D-Pyd cross-links are not found in skin collagen or procollagens and are not influenced by dietary collagen intake
- D-Pyd assay regarded as a sensitive and specific indicator of bone loss due to osteoporosis
- presence in the urine of higher than normal amounts of D-Pyd indicate a rapid rate of bone loss
- a high rate of bone turnover in an untreated postmenopausal woman indicates that bone loss is likely to be rapid

## Preventing oral-BIONJ before/during therapy

- Same strategy as with IV BPN use
- Concomitant medications:
  - prednisone and methotrexate increase risk for BIONJ and increase severity and reduce rate of response to drug discontinuation
  - ranitidine and other H2 blockers might increase risk for oral BIONJ because of increased absorption of BPN

## Prevention for oral BPNs < 3 years

- can be treated as any other patient
- Encourage smoking cessation
- Limit alcohol intake
- within the 3-year period remove non-restorable teeth, do perio surgery ASAP (and non-invasive procedures)

## Prevention for oral BPNs > 3 years

- Smoking cessation
- Limit alcohol intake
- Regular dental checks
- Eliminate dental disease conservatively

## Drug holidays

- consult prescribing physician to request temporary stop on oral BPN (drug holiday)
- extended drug holidays from oral BPNs up to 5 years – no increased incidence of osteoporosis-related fractures
- dentist should not discontinue the oral BPN; substitutes for BPNs include:
  - Raloxifene
  - recombinant human 1-34 parathyroid hormone
  - salmon calcitonin

## Treating established oral-BIONJ

- initial palliation then aim for spontaneous resolution, or resolution after débridement surgery
- Reinforce that osteoporosis-related fractures are painful and disabling - BPN therapy is beneficial in prevention
- Encourage regular physician follow up to monitor osteoporosis

## Treating established oral-BIONJ

- prevent pain with regular 0.12% chlorhexidine 30-mL swish-and-spit
- drug holiday if possible – for 6 months
- if pain or infection present, Rx antibiotics

## Outcome of established oral-BIONJ

- 40% of oral BIONJ cases resolve without débridement
- 60% of oral BIONJ cases show clinical and radiographic signs of improvement:
  - loosening or separation of necrotic bone from adjacent healthy bone
  - a radiographic involucrum separating a sequestrum from adjacent bone

## Summary

- nitrogen-containing BPNs pose a risk, related to:
  - route of administration
  - potency of the BPN
  - duration of use
- IV BIONJ is largely permanent, but most cases can be prevented or managed if they develop
- only a few cases require resection for resolution
- oral BIONJ cases are preventable
- most oral BIONJ cases resolve with a drug holiday either spontaneously or via simple débridement