PBL
Application of Biochemistry in dental practice

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Biochemistry Interaction with Oral & Systemic Diseases

Periodontal disease
Jaw Bone Necrosis
due to Bisphosphonate

Paget`s Disease
Osteoporosis
pathogenesis of Patient Condition presented with:

Osteonecrosis of the jaw bone due to Bisphosphonate
Patient’s Data

- 54 year old male presented with severe periodontal disease, type 2 diabetes, lung cancer treated with Bisphosphonate
Patient referred to his Dentist for oral evaluation during cancer therapy. Dentist referred him to Periodontist to evaluate periodontal condition. Periodontist referred him to Oral Surgeon. Oral Surgeon performed for full mouth extractions due to severe periodontal condition.

This leads to severe **osteonecrosis** of the maxillary and mandibular alveolar ridges.
Osteonecrosis of jaw bone due to Bisphosphonate
Why Bisphosphonate causes such a severe Osteonecrosis & Why it was used?
Why Bisphosphonate was given to this patient?

- Bisphosphonate (Aredia or Zometa®) are used to control
  - Bone metastases from lung cancer
  - Hypercalcemia due to bone metastasis
Common uses of Bisphosphonate

<table>
<thead>
<tr>
<th>Oral Forms</th>
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<tr>
<td>• Prevention and treatment of osteoporosis in postmenopausal women</td>
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<tr>
<td>• Increase bone mass in men with osteoporosis</td>
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<tr>
<td>• Glucocorticoid-induced osteoporosis</td>
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<tr>
<td>• Paget’s disease of bone</td>
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<td>• Osteogenesis imperfecta</td>
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<th>Intra-venous Forms</th>
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<tr>
<td>• Hypercalcemia of malignancy</td>
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<tr>
<td>• Bone metastases of solid tumors</td>
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<tr>
<td>• Breast and prostate carcinoma; other solid tumors</td>
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<td>• Osteolytic lesions of multiple myeloma</td>
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Relative Potency & Effect of Bisphosphonates

- Etidronate (Didronel)  1
- Tiludronate (Skelide)  10
- Pamidronate (Aredia)  100
- Alendronate (Fosamax)  1,000
- Risedronate (Actonel)  10,000
- Ibandronate (Boniva)  10,000
- Zolendronic acid (Zometa)  >100,000
US Surgeon General Report recommends a pyramidal approach to osteoporosis treatment

- Pharmacotherapy
- Address Secondary Causes Of Osteoporosis
- Lifestyle Changes
Osteoporosis & Fracture Risk
Paget’s Disease
Paget’s Diseases

- Characterizes by increased bone mass & density
- Abnormal bone remodeling
- Enlarged head and jaw bones
- Patient frequently change hat, eyeglasses, and dentures
- Cotton-wool appearance in the radiograph
- Loss of sight and hearing
- High Alkaline Phosphatase
Bisphosphonate therapy for Paget's disease

• Rendina et al. NEJM 353:24, 2005
Bisphosphonate
Basic Chemical Composition

- **Pyrophosphate compound**
  Essential for normal cellular functioning as it incorporate in ATP

- **Substitution of Carbon for Oxygen**
  Resistance to hydrolysis
  Bone matrix accumulation
  Extremely long half-life

- **Nitrogen-containing side chain**
  Increases potency, toxicity
  Direct link to BIONJ cases
Chemical Structure

Pyrophosphate (PPi)
(ATP = AMP + PPi)

Bisphosphonate
(P-C-P)
Bisphosphonate Structure

When $R'$ is an OH group binding to hydroxyapatite is enhanced.

The P-C-P group is essential for biological activity.

The R2 side chain determines potency.

P-C-P acts as 'bone hook' and is essential for binding to hydroxyapatite.
Bisphosphonate Structure

Nitrogen Side Chain
- Alendronate (Fosamax)
- Risedronate (Actonel)
- Ibandronate (Bonviva)
- Zolendronate (Zometa)
- Pamidronate (Aredia)

Non Nitrogen Side Chain
- Etidronate (Didronel)
- Clondronate (Bonefos)
- Tiludronate (Skelid)
Understanding Pathogenesis of Bone Necrosis
Understanding the pathophysiology of Bone Remodeling
Bone remodeling as Tissue Organ & System

**Tissue**
Haversian (osteons) which are aligned to withstand biofunctional challenges

**Organ**
Mandible
Tibia

**System**
Interacate with endocrine, renal, vascular & GI systems
Effects of other systems in Bone Remodeling

Endocrine System

Understanding Pathogenesis of Bone Necrosis
Biochemistry of Bisphosphonates

Inhibition of farnesyl diphosphate synthase in the osteoclasts

Metabolized to toxic analogue of ATP (non-nitrogen containing Bisphosphonate)
Bisphosphonate Causes The Following

1. Disruption of normal bone turnover
2. Compromised bone blood flow
3. Antiangiogenic
4. Mucosal toxicity
5. Local Environments of the Oral Cavity
Pharmacokinetics
Rapid accumulation in sites of increased bone deposition
Not metabolized (nitrogen containing)
Repeated doses accumulate in bone

*Bone ½ life of “years” – maybe a lifetime.*

Removed only by osteoclast-mediated resorption

“Biologic Catch 22”
Normal Bone Remodelling

Osteoclast → Osteoblast

- Bone Resorption
- Growth Factors
- Bone Formation

20 days → 160 days
Bone Metabolism

DIRECTION OF REMODELLING

OSTEOBLASTS

NEW BONE (OSTEOID)

OSTEOCLASTS

BONE FORMATION

BONE RESORPTION
1. Osteoclast actively reabsorbs bone matrix

2. BISPHOSPHONATE (☀) binds to bone mineral surface

3. BISPHOSPHONATE is taken up by the osteoclast

4. Osteoclast is inactivated

5. Osteoclast becomes apoptotic (‘suicidal’) and dies
Biologic Action of Bisphosphonates

- **Osteoclastic toxicity**
  - Apoptosis
  - Inhibited release of bone induction proteins
    - BMP, ILG₁, ILG₂

  - Reduced bone turnover, resorption
  - Reduced serum calcium*

- Hypermineralization
  - *“sclerotic” changes in lamina dura of alveolar bone
Bisphosphonates Effects on Osteoclasts


- Bisphosphonate attaches to exposed bone mineral surfaces
- Osteoclast takes up bisphosphonate → loss of ruffled border, inactivation, detachment

New bone formation by osteoblasts renders bisphosphonate inert, inaccessible

Lining cells
Osteoclast precursors
Osteoclast
Inactivated osteoclast
Bisphosphonate
Osteoblast
contributes to his severe osteonecrosis?

• Does hyperglycemia (increased blood sugar) alone influenced his osteonecrosis?

• Does abnormal metabolic changes in the glucose and ultimately protein and lipid metabolisms influenced his osteonecrosis?
Conclusion

- In this patient the combination of hyperglycemia, ketoacidosis, Steroid, Bisphosphonate, chemotherapy and his lung cancer resulted in reduced blood supply, impaired tissue function and reduced vascularity which resulted in severe periodontal disease. Osteonecrosis subsequent to tooth extractions were due to IV bisphosphonate use.