The Orthopedic Implications Of Prolonged Bisphosphonate Therapy In Osteoporosis

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Orthopedic Implications Of Osteoporosis

Introduction

• Osteoporosis Most Common Metabolic Bone Disease Worldwide
• Silent Disease – Bone Loss Occurs Without Symptoms
• Physician Recognition Following Fragility Fractures Is Low (USA)

Orthopedic Implications Of Osteoporosis

Introduction

• Osteoporosis Is The Absolute Reduction In Bone Volume And Mass
• The Bone Is Otherwise Normal
• Loss Of Mechanical Strength
• Leads To Fragility Fractures
Orthopedic Implications Of Osteoporosis

Introduction

• High Levels Of Awareness
• Promoted On Television
• News Media Coverage
• 10% Of Women > Age 55 Years In The USA Take "Medication" To Prevent Fractures

Burden Of Disease

• Life Time Risk Of Fragility Fractures In Women 40%-50%
• Life Time Risk Of Fragility Fractures In Men 13%-22%
• Worldwide 25 Million Fragility Fractures Annually
• Fragility Fractures Result In
  • Increased Morbidity & Mortality
  • Loss Of Quality Of Life

Fragility Fractures

• Pathologic Fx 2° To Weak Bone
• Defined As A Fall From Standing Height Or Less
  • Vertebral Compression Fx
  • Hip Fracture
  • Distal Radius Fracture
  • Proximal Humerus Fracture
Fragility Fractures
Epidemiology > 65 Years

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<th>2nd</th>
<th>3rd</th>
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<tr>
<td>Hip</td>
<td>Distal Radius</td>
<td>Proximal Humerus</td>
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Orthopedic Implications Of Osteoporosis
Demographics

- Yearly Cost Of Fragility Fx's > $20B
- 400,000 Hip Fractures / Yr USA
  - 25% End Up In Nursing Home
  - 50% Do Not Regain Pre-Injury Activity
  - 25% Die Within One Year
  - $ 50K In The First 90 Days

Osteopenia - Osteoporosis
Treatment Strategies

- Diet & Exercise
- Calcium & Vitamin D
- Non-Invasive Screening
- Pharmacologic Treatment
Osteopenia - Osteoporosis
Treatment Strategies

• Pharmacological Rx Indicated
  • Metabolic Abnormalities Corrected
  • DEXA Scores < 2.5 (Osteoporosis)
  • Calcium & Vit D Rx Without Success
  • Prior Fragility Fracture

Pharmacologic Treatment Strategies

• Bisphosphonates
  • Cornerstone Of Prevention & Treatment Of Fragility Fractures
  • Effective In Reducing Risk Of Fragility Fractures
  • GI Side Effects
  • Compliance Issues

Pharmacologic Biochemistry

• Bisphosphonates
  • Long Acting Powerful Anti-Resorptive Agents
  • High Affinity For Hydroxyapatite
  • Bone Density Maintaining Drug
  • Normalize Elevated Serum Bone Turnover Markers
Bisphosphonate Therapy
Chemical & Molecular Structure

- Two General Categories
  - Simple Diphosphonates
  - Amino Disphosphonates
  - Nitrogen / Amino Form is 10 to 10,000 Times More Potent Than Simple Form

<table>
<thead>
<tr>
<th>Subclass &amp; Generic Name</th>
<th>Brand Name &amp; Manufacturer</th>
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<tr>
<td>Nitrogen Containing Bisphosphonates</td>
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<tr>
<td>Alendronate</td>
<td>Fosamax, Merck</td>
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<tr>
<td>Ibandronate</td>
<td>Boniva, Roche</td>
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<tr>
<td>Pamidronate</td>
<td>Aredia, Novartis</td>
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<tr>
<td>Etidronate</td>
<td>Didronel, Proctor &amp; Gamble</td>
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<tr>
<td>Tiludronate</td>
<td>Skelid, Sanofi Avendis</td>
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Bisphosphonate Therapy
Indications

- Heritable Skeletal Disorders
- Hypercalcemia
- Metastatic Bone Disease
- Multiple Myeloma
- Pagets Disease
- Osteoporosis
Bisphosphonate Therapy
Osteoporosis

- Most Commonly Used Class Of Drugs To Treat Osteoporosis Worldwide
- Prolonged Therapy Alters Normal Bone Remodeling
- Atypical Femur Fractures
- Uncertainty & Debate Regarding Duration Of Rx

Bisphosphonate Therapy
Bone Physiology

- Bone Resorption And Remodeling Are Coupled & Balanced
- Mediated Thru TGF – B
- TGF- B Necessary for Migration Of Stem Cells To Sites Of Resorption
- When Bone Resorption Is Halted Stem Cells May Not Be Able To Travel To Sites Of Bone Repair

Bisphosphonate Therapy
Pharmacokinetics

- Bisphosphonates Bind To HA Crystals In Bone
- Trapped As New HA Crystals Form
- Activated Osteoclasts Take Up Bisphosphonates As They Resorb Bone
- 50% - 75% Of Bisphosphonates Are Cleared
- Remaining 25% - 50% Incorporated Into Bone
- Half Life 5-10 Years
**Bisphosphonate Therapy**

**Mechanism Of Action**

- Inhibit Osteoclastic Function &
- Induces Osteoclastic Apoptosis By Interfering With Protein Prenylation & Inhibiting The Mevalonate Pathway Of Cholesterol Synthesis

**Bisphosphonate Therapy**

**Reduction In Risk Of Osteoporotic Fracture**

- Multiple RCT Have Shown Bisphosphonates Increase Bone Mineral Density (BMD) And Decrease The Risk Of Fracture

**Bisphosphonate Therapy**

**Literature Review**

- Fracture Intervention Trial (FIT)
- Fracture Intervention Trial Long Term Extension (FLEX)
- Health Outcome Reduced Incidence Zoledronic Acid Pivotal Fracture Trial (Horizon)
**Fracture Intervention Trial (FIT)**  
N = 6400 Women

Prospective, Double Blind, Randomized Multi-Center Trial Comparing Alendronate & Calcium To Calcium Alone

**Results & Conclusions**
- Maintained BMD Throughout The Body
- Decreased The Incidence Of Fragility Fractures
  - Hip 51%, Distal Radius 44%, Vertebral 46%

- Lancet 348: 1535-1541, 1996
- JAMA 280: 2077-2082, 1998

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1099 Treated With Alendronate For 5 Yrs 5 mg, 10 mg, Placebo (FIT)

- Women Who Stopped Rx After 5 Yrs Showed A Moderate Decline In BMD But No Higher Risk Of Fracture Compared To Those Who Continued Treatment

**Conclusion:** Stopping Therapy For Up To 5 Years Does Not Appear To Significantly Increase Fracture Risk

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**Health Outcomes & Reduced Incidence Of Fracture With Zoledronic Acid Pivotal Fracture Trial (Horizon)**

Randomized Double Blind Placebo Controlled Trial Of
- 2127 Patients Received Yearly Zoledronic Acid Or Placebo Within 90 Days Of A Hip Fracture

- 35% Reduction In Incidence Of A Second Fracture
- 28% Reduction In Death From Any Cause
- No Adverse Effects On Fracture Healing

Bisphosphonate Therapy
Reduction in Risk of Osteoporotic Fracture

• These Studies Led To FDA Approval Of Bisphosphonates For The Rx Of Osteoporosis In 1990’s
• 10 Year Results Showed Good Safety & Efficacy
• But Wait – The Story Continues

Bisphosphonate Therapy
Atypical Femur Fractures

• In 2004-2005 Reports Emerged About A New Fracture Pattern Associated With Prolonged Bisphosphonate Use
• Term Atypical Femur Fracture Was Adopted To Identify This Unique Entity

Bisphosphonate Therapy
Atypical Femur Fractures

• Paradox Of Treatment
• Medication Designed To Prevent Bone Loss & Fractures Has An Apparent Contradictory Effect
Prolonged Bisphosphonate Therapy
Why The Femur?

The Proximal Femur Is Subjected To
The Highest Stresses In The Body
& One Of The Adaptations To Such
Forces Is The High Concentration
Of Cortical Bone In The Region

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Prolonged Bisphosphonate Therapy
Key Point

Long Term Suppression Of
Normal Bone Remodeling
Increases The Risk Of
Fracture Particularly In The
Areas Of Greatest Tensile
Strength ie Femur (800psi)

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Prolonged Bisphosphonate Therapy
Atypical Femur Fracture

A Bisphosphonate Related Lesion
Represents A Brittle Stress Fracture
In The Femur With No Plastic
Deformation Prior To Failure
Prolonged Bisphosphonate Therapy
Atypical Femur Fracture

- This Stress Fracture Is The Result Of
  - Increased Mineralization
  - Heterogeneity Of Mineralization
  - Altered Rates Of Bone Turnover
  - Microdamage Accumulation
  - Altered Collagen Cross-Linking

Prolonged Bisphosphonate Therapy
Femur Fractures

- Unique Clinical And Radiographic Features
- New Onset Hip Or Thigh Pain In Patients On Bisphosphonates Mandates Imaging Of The Hip & Femur

Bisphosphonate Therapy
Femur Fractures

- Clinical Presentation
  - Hip, Groin, Thigh Pain
  - Pain In Absence Of Trauma
  - Bilateral Symptoms Common
  - Prodromal Pain 50% - 70%
  - Younger Than Typical Hip Fracture Patient
Bisphosphonate Therapy
Femur Fractures

- Clinical Presentation
  - Virtually All In Women
  - More Common In Caucasians And Asians
  - Higher BMI's
  - Often On Steroids Or Statins
  - T-Scores -1.5 to -2.0 Range

Bisphosphonate Therapy
Femur Fractures

- Differential Diagnosis
  - Osteoarthritis Of The Hip
  - Trochanteric Bursitis
  - Atypical Sciatic
  - Spinal Stenosis
  - Myositis
  - Tumor

Prolonged Bisphosphonate Therapy
Radiographic Findings

- **Stage 1**
  - Cortical Thickening Lateral > Medial
  - Flaring (Beaking) Of The Lateral Cortex
  - Increased Bowing Of The Femur

- **Stage 2**
  - Lucent Line (Stress Fracture)
  - Uni-Cortical Vs Bi-Cortical (Dreaded Black Line)

- **Stage 3**
  - Complete Fracture
Prolonged Bisphosphonate Therapy

Stage 1
- Cortical thickening

Stage 2
- Incomplete Fracture

Stage 3
- Complete Fracture

Typical Proximal Femur Fracture In Elderly
- Slightly Older Age Group
- Spiral Fracture Pattern
- Some Comminution
- Cortical Thinning

Atypical Proximal Femur Fracture In Elderly
- Slightly Younger Age Group
- Transverse Or Short Oblique Fracture Pattern
- Little Or No Comminution
- Cortical Thickening
Prolonged Bisphosphonate Therapy
Treatment Stage 1

- Stop Bisphosphonates!
- Protective Wt. Bearing
- Correct Calcium & Vitamin D
- Warn Pts Of Risk Of Fracture!
- Consider Forteo (PTH)
- If No Improvement In 2-3 Months Consider IM Nailing

Prolonged Bisphosphonate Therapy
Treatment Stage 2

- Incomplete Stress Fracture
- Almost All Very Symptomatic
- High Risk Of Fracture
- Prophylactic Nailing !!!
- Switch To PTH (Forteo)
Prophylactic Nailing

79 Year Old Asian Female; 8 Yrs On Alendronate

Prolonged Bisphosphonate Therapy
Treatment Stage 3

- Complete Fracture
- Surgical Urgency
- Medical Co-Morbidities
- Intra-Medullary Nailing
- Technical Issues

Prolonged Bisphosphonate Therapy
Treatment Stage 3

- IM Nailing Treatment Of Choice
- Slower Healing
- Higher Incidence Of Non-Union
- Technical Issues
  - Femoral Bowing
  - Thickened Cortices
  - Narrow Canal
Prolonged Bisphosphonate Therapy

Technical Challenges

- Technical Issues
  - Femoral Bowing
  - Thickened Cortices
  - Narrow Canal
  - Special Reamers
  - Slow Healing

Park-Wyllie et al.: Bisphosphonate Use And The Risk Of Subtrochanteric Or Femoral Shaft Fractures In Older Women

Conclusions

1. Bisphosphonate Therapy Significantly Decreases The Risk For Femoral Neck Or Intertrochanteric Hip Fractures
2. Only In Patients Taking Bisphosphonates > 5 Years Do Atypical Fractures Substantially Increase. In The Two Years Following Five Years Of Treatment; One in 500 May Sustain A Fracture
3. Atypical Fractures Are Uncommon & Data Supports Bisphosphonate Therapy

JAMA 305: 783-789, 2011

Prolonged Bisphosphonate Therapy

Kaiser California Experience

1,835,115 Patients Rx Bisphosphonates 2007-2011

142 Atypical Femur Fractures Of Whom 128 On Bisphosphonate

Age Adjusted Incidence

1.78 / 100,000 Years With Exposure Up To Two Years
113 / 100,000 Years With Exposure Between 8 – 10 Years

Incidence Of Hip Fractures Declined By 30% And The Benefits Of Bisphosphonate Therapy Is 100 fold Greater Than The Risk Of Atypical Femur Fracture
Bawa HS, Weick J, Dirschl D: Anti-Osteoporotic Therapy After Fragility Fracture Lowers The Rate Of Subsequent Fracture
JBJS 97: 1555-1562, 2015

Database Analysis Of 31,069 Patients Who Sustained A Fragility Fracture

10.6% Of Patients Were Place On Anti-Osteoporotic Therapy Following Their Index Fracture

3 Year Fracture Rate Was 7.5% in The Treatment Group & 9.7% in The Non-Treatment Group

Conclusion: Anti-Osteoporotic Rx Reduces The 3 Yr Risk Of A Subsequent Fracture By 40% & Can Prevent A Subsequent Fracture In One Of Every Twenty-Seven Patients Treated

Prolonged Bisphosphonate Therapy
Conclusions

- Very Strong Relationship Between Bisphosphonates & Atypical Femur Fractures
- Cephalomedullary Nailing Rx Of Choice
- Delays In Healing 10%-25%
- Duration Of Treatment Remains Controversial
- Current Protocol 5 Yrs Than Drug Holiday

Prolonged Bisphosphonate Therapy
Conclusions

- Solicit Info On Hip Or Thigh Pain
- Is Patient On Bisphosphonates?
- X-Rays Are Mandatory
  - Early Changes Are Subtle
  - Cortical Thickening / Beaking
  - MRI Very Sensitive
  - X-Ray Contra-Lateral Side
Prolonged Bisphosphonate Therapy
Conclusions

- Flawed Perception That These Drugs Are “Health Supplements” With Minimal Adverse Effects
- Long Term Retention In Bone
- Persistence Of Their Effect After Stopping Therapy
- Drug “Holiday” For Low To Moderate Risk Patients

It Is Not Enough To Stare Up The Steps; We Must Step Up The Stairs

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83 Yr Female On Fosamax For 10 Years. Missed Step & Fell. Classic Atypical Femur Fracture
Post-Op Closed Intra-Medullary Nailing

Distracted?

2 Year Follow-Up; Healed; Asymptomatic

16 Months S/P IM Nailing Of Atypical Femur Fracture

Dynamized
67 Yr Female Fell On Alaskan Cruise Sustaining A Femur Fracture

12 Months Post-Op; Mild Residual Pain; Healed

Revision ORIF With Compression, Lag Screw, & BMP
5.5 Year History Of Bisphosphonate Use

Emergency Surgery In A Small Town In Alaska With Trochanteric Entry Nail Supine On A Fracture Table

Interim History

Returns To Los Angeles At 3 Weeks
Seen By Her Family Doctor
Wound Clean & Dry Sutures Removed
Diagnosed With DVT & Placed On Coumadin
Physical Therapy & Ortho On Hold
Referred At 9 Weeks Post-Op With These Radiographs

15° Varus
40° Anterior Angulation

How Would You Manage This Problem Now?

1. Revision Nailing
2. Blade Plate
3. Prox Femur Locking Plate

Lateral Decubitus On A Fracture Table
Reamed Piriformis Entry Reconstruction Nailing
Pre-Op
Post-Op