Pharmacology: Therapeutics of Calcium Metabolism

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Outline of Lecture

- Hypercalcemia
- Hypocalcemia
- Osteoporosis

CAUSES OF HYPERCALCEMIA

- Primary Hyperparathyroidism
- Malignancy
- Other endocrinopathy
  - Hyperthyroidism
  - Pheochromocytoma
  - VIPoma
- Adrenal insufficiency
- Medications
  - Lithium
  - Thiazide diuretics
  - Thyroid hormone
  - Vitamin A
  - Vitamin D
- Vitamin D Toxicity
- Granulomatous disease
  - Tuberculosis
  - Sarcoidosis
- Any other
- Lymphoma
- FH
- Immobilization
- Acute or chronic renal disease

Clinical Features of Hypercalcemia

- Constitutional
- Central nervous system
- Gastrointestinal tract
- Renal
- Cardiovascular

Factors That Influence Symptomatology in Hypercalcemia

- Serum calcium concentration
- Rate of rise
- Duration
- Individual variability

Pathophysiologic Features of Acute Hypercalcemia

I. New or Existing Stimulus to Hypercalcemia
- Osteoclast activation virtually always present
- Renal tubular conservation of calcium (PTH, PTHRP)
- GI hyperabsorption of calcium (less important)
- Reduced mobility
II. Hypercalcemia Becomes Symptomatic
- Polyuria
- Polydypsia
- Anorexia
Pathophysiologic Features of Acute Hypercalcemia

III. Worsening Hypercalcemia
- Reduced fluid intake
- Continued polyuria
- Dehydration

IV. Reduced Plasma Volume
- Impaired renal function
- Reduced renal calcium clearance
- Rapidly worsening hypercalcemia

At What Level Should Hypercalcemia Be Treated Emergently?*

• < 12 mg/dL ?
• 12-14 mg/dL ?
• >14 mg/dL ?

*Typical nl range 8.4-10.2 mg/dl

General Management of Hypercalcemia

- Intravenous rehydration
- Saline administration
- Diuresis with furosemide
- Dialysis (if necessary)
- Mobilization

Management of Hypercalcemia

General
- Rehydration
- Saline Administration
- Diuresis with Furosemide
- Dialysis
- Mobilization

Specific
- Bisphosphonates
- Plicamycin
- Calcitonin
- Gallium Nitrate
- Phosphate
- Glucocorticoids
- Therapy of Underlying Etiology

Bisphosphonates
Bisphosphonates For Acute Hypercalcemia

- Osteoclast inhibitors
- Intravenous route necessary
- Reduction in serum calcium begins 24-36 hours after first dose
- Duration of effect is variable

Adverse Effects of Parenteral Etidronate for Hypercalcemia

Hypocalcemia ("overshoot")

Zoledronate vs. Pamidronate For Hypercalcemia

Mean Corrected Serum Calcium C at baseline and days 4, 7, and 10 after treatment of hypercalcemia with (•) zoledronic acid 4mg, (◦) zoledronic acid 8mg, or (△) pamidronate 90mg.

Major et al, J Clin Oncology, 2001
Management of Hypercalcemia

**Zoledronate vs. Pamidronate**

<table>
<thead>
<tr>
<th></th>
<th>Zoledronate</th>
<th>Pamidronate</th>
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<tr>
<td>Days</td>
<td></td>
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**Adverse Effects of Pamidronate and Zoledronate**

- Mild, transient fever (<2°C)
- Transient leukopenia
- Small reduction in the serum phosphate
- Hypocalcemia (“overshoot”)

**Management of Hypercalcemia**

**General**
- Rehydration
- Saline Administration
- Diuresis with Furosemide
- Dialysis
- Mobilization

**Specific**
- Bisphosphonates
- Plicamycin
- Calcitonin
- Gallium Nitrate
- Phosphate
- Glucocorticoids
- Therapy of Underlying Etiology

**Plicamycin**

- Potent osteoclast inhibitor
- Intravenous, daily for up to 5 days
- Reduction in serum calcium begins 12-24 hours after first dose
- Duration of effect is variable

**Adverse Effects of Plicamycin**

- Hypocalcemia (“overshoot”)
- Hepatic toxicity
- Nephrotoxicity
- Bone marrow toxicity (platelets)
Management of Hypercalcemia

**General**
- Rehydration
- Saline Administration
- Diuresis with Furosemide
- Dialysis
- Mobilization

**Specific**
- Bisphosphonates
- Plicamycin
- Calcitonin
- Gallium Nitrate
- Phosphate
- Glucocorticoids
- Therapy of Underlying Etiology

**Calitonin For Hypercalcemia**
- Osteoclast inhibitor
- Calciuretic
- IV or SC, Q12 hours
- Rapid reduction in calcium (within 12 hours)
- Weak and short-lived effect

**Calcitonin in the management of hypercalcemia**

Calcitonin in the management of hypercalcemia

**The Most Rapidly Acting Agents For Hypercalcemia**

Calcitonin>Plicamycin>Bisphosphonates

**Combination Therapy For Hypercalcemia**

- Use of a rapidly acting agent (calcitonin)
- Simultaneous with a more potent, but more slowly acting agent (bisphosphonate)
## Management of Hypercalcemia

### General
- Rehydration
- Saline Administration
- Diuresis with Furosemide
- Dialysis
- Mobilization

### Specific
- Bisphosphonates
- Plicamycin
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- Gallium Nitrate
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- Therapy of Underlying Etiology

## Management of Hypercalcemia

### General
- Rehydration
- Saline Administration
- Diuresis with Furosemide
- Dialysis
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### Specific
- Bisphosphonates
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- Calcitonin
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- Glucocorticoids
- Therapy of Underlying Etiology

## Outline of Lecture

- **Hypercalcemia**
- **Hypocalcemia**
- **Osteoporosis**

## Clinical Features of Hypocalcemia

- Neuromuscular irritability
- Paresthesias (numbness and tingling)
- Chvostek’s sign
- Trousseau’s sign
- Prolonged Q-T interval
- Carpal, pedal, broncho, or laryngeal spasm
- Seizures

## Clinical Features of Hypocalcemia

**Determinants of signs and symptoms**

- Extent of hypocalcemia
- Rapidity of reduction
- Duration of hypocalcemia

## Management of Hypocalcemia

### Indications for Acute Treatment

- Symptoms
- No symptoms but...
  - Serum calcium (corrected for serum albumin) <7.5 mg/dL
  - History of seizures
  - Previous compression fracture
Emergency Management of Hypocalcemia

Intravenous Preparation of Choice

✓ Calcium gluconate
× Calcium chloride (do not use)

FOR IMMEDIATE RELIEF OF SYMPTOMS:

1-2 amps of 10% calcium gluconate (93 mg of elemental calcium/amp) intravenously over 10-15 minutes

Emergency Management of Hypocalcemia

To raise the serum calcium by 2-3 mg/dl:

10-15 mg/kg of calcium intravenously (in 1 liter of D$_5$W) over 6-8 hours

Example:
70 kg individual
15 mg/kg = 1050 mg calcium

Amps of 10% calcium gluconate = 1050 mg/93 mg/10 ml

Approximately 11 amps

Management of Chronic Hypocalcemia

• Underlying etiology
• Oral calcium
• Oral Vitamin D

CALCIUM CONTENT OF MEDICINAL SALTS

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<th>Source</th>
<th>Calcium Content (mg/g)</th>
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<td>200</td>
<td>20%</td>
</tr>
<tr>
<td>Lactate</td>
<td>128</td>
<td>12.8%</td>
</tr>
<tr>
<td>Gluconate</td>
<td>88</td>
<td>8.8%</td>
</tr>
<tr>
<td>Glubionate</td>
<td>65</td>
<td>6.5%</td>
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Management of Chronic Hypocalcemia

• Underlying etiology
• Oral calcium
• Oral Vitamin D
  • Nutritional (400-800 IU daily)
  • Pharmacological (>1000 IU day)
Outline of Lecture

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- Hypocalcemia
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- How much?
- How much at a time?
- What form?
- Brand vs generic vs fancy?
- When?
- With food or without food?

Nonpharmacological Approaches to the Management of Osteoporosis*

- Calcium
- Vitamin D
- Exercise
- Lifestyle (Smoking, Alcohol, etc)
- Fall Prevention

*Recommended for virtually everyone!
Approved Pharmacologic Therapies in the United States for Osteoporosis

- Hormone replacement therapy (HT)
-Raloxifene
- Bisphosphonates
  - Alendronate
  - Risedronate
  - Ibandronate
  - Zoledronate
- Calcitonin
- Teriparatide [humanPTH(1-34)]

Estrogen Reduces the Risk of All Clinical Fractures

E+P: N=16,000 women ages 45-79
Mean age: 63.2
Placebo or estrogen+progestin
CEE arm: N=10,739 ages 50-79
Mean age: 63.6
Placebo or CEE 0.625 mg daily
Fractures: All clinical fractures (less than 10% were vertebral fractures)
Treatment intervals: E+P 5.2 years; CEE 6.8 years

Risk Benefit

- Venous Thromboembolic Events (VTE) 4% increase
- Coronary Artery Disease 20% increase
- Colon Cancer 29% increase
- Breast Cancer 26% increase
- Stroke 41% increase
- Venous Thrombolic Events (VTE)
- Fracture Reduction

Threshold Level
Early STOP=Clear Harm

Threshold Level
Early STOP=Clear Benefit

WHI: Conclusions regarding the skeleton*

- Estrogen should not be used as a primary therapy to prevent bone loss
- Estrogen should not be used as a primary approach to the treatment of osteoporosis

*This is a very controversial issue!
**Raloxifene: A Selective Estrogen Receptor Modulator**

**Basic Side Chain**

Estrogen Antagonist (uterus, breast)

- Benzothiophene moiety
- Estrogen Agonist (bone, lipids)
  - BMD (bone mineral density) increase
  - Decrease in total and LDL cholesterol

**Effects of Raloxifene on BMD:**

**Effects of Raloxifene on New Vertebral Fractures: The MORE Trial – 36 Months**

- **Benefits**
  - Improved bone mass
  - Reduced number of vertebral fractures
  - No breast tenderness
  - No uterine bleeding or spotting
  - Reduced risk of breast cancer*
  - No increased cardiovascular risk

- **Disadvantages**
  - Increased hot flashes
  - Increased leg cramps
  - Increased risk of DVT and pulmonary embolism

*New indication, 2007

**RALOXIFENE**

- Well-absorbed from the GI tract
- Can be taken any time
- Once daily medication (60 mg)
- With or without food
- No contraindications in women with upper gastrointestinal symptoms


*Not FDA-approved dose.*
Osteoporosis Therapy: Calcitonin

- **Calcitonin 200 units daily by nasal spray**
- **Indication:** treatment of postmenopausal osteoporosis
- **Effects**
  - Very small effect (1-2%) on bone density in spine
  - No effect on bone loss in women within 5 years of menopause
  - Reduced incidence of vertebral fractures (36%) in women with pre-existing vertebral fractures
  - No effect on non-vertebral or hip fractures has been observed
- **Side effects:** nasal stuffiness
- **Contraindications:** hypocalcemia, allergy to calcitonin, pregnancy, recent menopause (<5 years)

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**BISPHOSPHONATES APPROVED IN THE US FOR USE IN OSTEOPOROSIS**

- **Alendronate**
- **Ibandronate**
- **Risedronate**
- **Zoledronate**

**Oral bisphosphonates**

- Poorly absorbed (<1.0%)
- Specific requirements for optimal oral absorption:
  - Fasting state with plain water only
  - Must be upright
  - No food or drink for at least 30 minutes (for ibandronate, 60 minutes)
- Several half-lives:
  - Rapid uptake in bone and clearance by the kidney
  - Prolonged skeletal half-life (years)
- GI intolerance has occurred with orally administered amino-substituted bisphosphonates (alendronate, risedronate, ibandronate)
The Vertebral Fracture

Alendronate: Effect on vertebral fracture

Black DM et al. Lancet, 1996;348:1535-41

Clinical vertebral fracture
New morphometric fractures
Multiple morphometric fractures
* statistically significant

Risedronate (VERT:Multinational study)
Reduction in Relative Risk of New Vertebral Fracture Over Years 0-3 and Years 4-5


Ibandronate: new vertebral fractures – 2.5 mg daily (ITT)


Reclast Reduced 3-Year Risk of Morphometric Vertebral Fractures (Stratum I)

Ostman PO et al. Osteoporosis Int 2004;15:792-798
NON-VERTEBRAL FRACTURES

NONVERTEBRAL AND HIP FRACTURES
ALENDRONATE FRACTURE INTERVENTION TRIAL

After data from Black DM et al. Lancet 1996;348:1535-1541

NONVERTEBRAL AND HIP FRACTURES
RISEDRONATE VERT-NA

27 total hip fractures (control + primary treatment group)
NVFx = clavicle, humerus, forearm, pelvis, femur, lower leg; no consideration for trauma
After data from Harris ST et al. JAMA 1999;282:1344-1352

NONVERTEBRAL AND HIP FRACTURES
IBANDRONATE BONE STUDY

10 total hip fractures (control + primary treatment group)
NVFx = all except hands, feet, face, and skull
After data from Chesnut CH III et al. J Bone Miner Res 2004;19:1241-1249

NONVERTEBRAL AND HIP FRACTURES
ZOLEDRONATE HORIZON TRIAL.

140 total hip fractures
NVFx = excluding fingers, toes and facial bones
*P<0.05

ISSUES WITH BISPHOSPHONATES

• INCONVENIENT DOSING REQUIREMENTS (IF USED DAILY)
**Bisphosphonates: Weekly Dosing**

- Effects of weekly vs daily dosing on BMD and turnover are the same
- Extrapolation of fracture protection from daily studies is reasonable
- Has improved acceptance, but effect on adherence not known

![Graph showing BMD and turnover comparison](image)

**Bisphosphonates Other administration regimens**

- Monthly dosing
  - Ibandronate
  - Risedronate

- Intravenous dosing
  - Ibandronate (every 3 months)
  - Zoledronate (once yearly)

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**Adverse events with bisphosphonates for osteoporosis**

- Upper GI intolerance
- Acute Phase Reaction
- "Oversuppression of bone"\(^1\)
- Osteonecrosis of the jaw\(^2,3\)

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**Actions of anti-resorptive agents**

- Stabilize or increase BMD
- Maintain trabecular architecture
- Increase mineralization density of bone matrix

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**All Antiresorptive Therapies for Osteoporosis**

- Hormone replacement therapy (HT)
- Raloxifene
- Bisphosphonates
  - Alendronate
  - Risedronate
  - Ibandronate
  - Zoledronate
- Calcitonin

**Inhibit Bone Resorption**

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1. Odowu et al. J Clin Endocrinol Metab. 2005

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Approved Therapies in the United States for Osteoporosis

- Hormone therapy (HT)
- Raloxifene
- Bisphosphonates
  - Alendronate
  - Risedronate
  - Ibandronate
  - Zoledronate
- Calcitonin
- Teriparatide [human parathyroid hormone (1-34)]

Human Parathyroid Hormone

PTH as a Treatment for Osteoporosis: A Paradox

- How can PTH be a potential therapy for osteoporosis when the clinical disorder of chronic PTH excess, primary hyperparathyroidism, is associated with bone loss?

PTH and Dose Determine Effect on Bone

<table>
<thead>
<tr>
<th>Mode</th>
<th>Effect</th>
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<tbody>
<tr>
<td>Continuous (High Dose)</td>
<td>Catabolic</td>
</tr>
<tr>
<td>Daily (Low Dose)</td>
<td>Anabolic</td>
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Teriparatide reduces the incidence of Vertebral and Non-Vertebral Fractures in Postmenopausal Women with Osteoporosis

What do the bones actually look like after therapy with PTH?
Improved Trabecular Connectivity After hPTH (1-34) Therapy

Before
CD: 2.9/mm³

After
CD: 4.6/mm³


OSTEOPOROSIS

PREVENTABLE AND TREATABLE