Hypercalcemia

Definition

Hypercalcemia is a corrected total serum calcium or an ionised calcium above the normal range.

Distribution of Calcium

Calcium circulates in the blood stream in three different forms:
- 50% Ionised Calcium
- 40% Protein Bound Calcium
- 10% Complexed to Anions

Symptoms

- Mild hypercalcemia may be asymptomatic
- Moderate to Severe hypercalcemia
  - Anorexia
  - Nausea
  - Vomiting
  - Constipation
  - Nocturia
  - Abdominal Pain
  - Headache
  - Confusion / Drowsiness
Signs
- Dehydration
- Proximal myopathy
- Signs due to primary disease

Complications
- Sinus bradycardia
- Heart blocks
- Cardiac arrhythmias
- Nephrolithiasis
- Nephrogenic diabetes insipidus

Lab Evaluation of Hypercalcemia
- Ionised Calcium
- Phosphate
- PTH
- Vitamin D
  * 25 hydroxy and 1,25 dihydroxy

PTH Assay

Differential Diagnosis of Hypercalcemia
- Primary Hyperparathyroidism
- Malignancy
- Thyrotoxicosis
- Familial Hypocalciuric Hypercalcemia (FHH)
- Granulomatous Diseases
- Immobilization
- Milk Alkali Syndrome
- Drugs: Thiazides, Lithium
  Vitamin A & Vitamin D intoxication
Primary Hyperparathyroidism

Indications for Surgery
- Persistently elevated calcium, 1 mg above upper limit of normal range
- Renal calculi or nephrocalcinosis
- Hypercalciuria > 400 mg/day
- Reduction in bone density > 2.5 SD of peak bone mass
- Medical surveillance not suitable or desirable

Sestamibi Scanning in Hyperparathyroidism
- Two phase study shows very good accuracy
- Deep cervical and mediastinal glands also seen
- Useful in studying patients with recurrent or persistent disease
- False negative scans with small adenomas and hyperplasia

Malignancy Associated Hypercalcemia
- Humoral hypercalcemia of malignancy
- Local osteolytic hypercalcemia
- Ectopic hyperparathyroidism

Humoral Hypercalcemia of Malignancy
- PTHrP mediated:
  - Squamous cell cancer: Lung, esophagus, skin, head & neck
  - Breast carcinoma, renal cell Ca
  - Human T-cell leukemia virus-I
- 1, 25 Vitamin D mediated:
  - Lymphomas

Thyrotoxicosis
- Mild hypercalcemia in 25 – 50% of patients
- Direct effect of thyroid hormone on trabecular and cortical bone
- If calcium > 12.0, suspect coexistent hyperparathyroidism
Familial Hypocalciuric Hypercalcemia
- Autosomal dominant condition
- PTH level normal or high
- Calcium / Creatinine clearance is low (< 0.01)
- Hypercalcemia persists after subtotal parathyroidectomy

Calcium Sensing Receptor (CaSR)
- Parathyroid cells have receptors for calcium that affect PTH synthesis and release
- CaSR agonists activate the receptor and suppress PTH secretion in hyperparathyroidism
- Inactivating mutation of the CaSR gene is responsible for hypercalcemia in FHH

Vitamin D Mediated Hypercalcemia
- Granulomatous diseases
- Lymphomas
- Vitamin D toxicity

Sarcoidosis
- 10 % of patients hypercalcemic
- 30 % of patients hypercalciuric
- 1, 25 Vitamin D production by the macrophage in the sarcoid granuloma

Immobilization
- Calcium usually increases within normal range
- Overt hypercalcemia when there is an increased bone turnover rate
- Bisphosphonates can preserve bone mass

Milk Alkali Syndrome
- Excessive ingestion of calcium and alkali
- Normal to low serum phosphorus and metabolic alkalosis
- Hypocalcemia may develop with treatment
Drugs Causing Hypercalcemia

- Thiazides
  - Increases distal tubular reabsorption of calcium
  - Usually causes mild hypercalcemia
  - Suspect another disorder if hypercalcemia is severe or persists after thiazide withdrawal

Lithium

- Increases tubular reabsorption of calcium
- Increases PTH secretory set point
- Parathyroid hyperplasia or adenomas may be seen

Goals of Therapy

- Correct dehydration
- Enhance renal excretion of calcium
- Inhibit accelerated bone resorption
- Treat underlying disorder

Hydration

- First step in treatment of any hypercalcemic patient
- Increases calcium clearance
- Calcium drops by 1.6 – 2.4 mg

Loop Diuretics

- Inhibit calcium reabsorption in loop of Henle
- Only after volume expansion
- Prevent volume overload in patients with compromised cardiac function
Antiresorptive Therapy
- Bisphosphonates
- Calcitonin
- Gallium

Biphosphonates
- Etidronate, Pamidronate, Zoledronic acid, Alendronate and Risedronate
- Binds to hydroxyapatite and inhibits osteoclast action
- Oral absorption is poor
- Low grade fever, hypophosphatemia and myalgias

Etidronate vs Pamidronate
Gucalp et. al.
65 cancer patients with calcium > 12.0
- 60 mg of pamidronate as a 24 hour infusion – 70% response
- 7.5 mg/Kg Etidronate, 2 hour infusion for 3 day – 41% response

Effective Dose of Pamidronate
Nussbaum et. al.
50 cancer patients with calcium > 12.0
- Pamidronate as a 24 hour infusion
  - 30 mg (40% response)
  - 60 mg (61% response)
  - 90 mg (100% response)

Zoledronic acid
- Most potent agent for treatment of hypercalcemia
- 4mg IV infusion over 15 minutes

Zoledronic acid vs Pamidronate

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<thead>
<tr>
<th></th>
<th>Zoledronic Acid</th>
<th>Pamidronate</th>
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<tbody>
<tr>
<td>Dose</td>
<td>4 mg</td>
<td>90 mg</td>
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<tr>
<td>Efficacy</td>
<td>88%</td>
<td>70%</td>
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<tr>
<td>Duration of Calcium Control</td>
<td>32 days</td>
<td>18 days</td>
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Calcitonin
- 4-8 MRC Units/Kg every 6-12 hours, SC or IM
- Calcium drops within a few hours, maximum reduction in 12 – 24 hours
- Transient nausea, flushing or abdominal cramps

Gallium
- 200 mg/m² per day IV, maximum five days
- 60-86% normocalcemic in 96 hours
- Nephrotoxicity, pulmonary infiltrates, hypophosphatemia and optic neuritis

Glucocorticoids
- Useful in vitamin D toxicity, lymphomas, granulomatous diseases and multiple myeloma
- 200-300 mg hydrocortisone or its equivalent per day for 3-5 days

Combination Therapy with Calcitonin and Pamidronate

Thiebaud et. al.
- 17 cancer patients treated with IV Pamidronate and Calcitonin suppositories
  - Normal calcium by the third day
- 17 patients had IV Pamidronate alone
  - Normal calcium by the sixth day

Dialysis
Peritoneal or hemodialysis should be reserved for patients with hypercalcemia and renal failure

LR is a 54 y/o woman, who is two years postmenopausal, was noted to have a serum calcium of 11.4 on a routine chem-24. She was asymptomatic and was on no medications.

Intact PTH 64 (10-55)
Creatinine Clearance: 80
Urinary Ca: 210 (< 250)
Bone Density: normal
Abdominal X-ray: normal
Mild Hypercalcemia in Hyperparathyroidism (10.5 – 12.0)
- In the presence of symptoms or complications
- Parathyroid surgery
- In asymptomatic hypercalcemia
  - Hydration, moderate calcium diet
  - Drugs: Bisphosphonates, Estrogen

Monitoring of Asymptomatic Patients with Hyperparathyroidism
- Serum calcium every six months
- Serum creatinine yearly
- Bone mineral density yearly

BK is a 27 y/o woman with severe headaches, nausea, and weakness. She is noted to be dehydrated. She has a scar at the base of her neck.

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Calcium 13.2
P 4.8
Intact PTH 6.0 (10-55)
25 Vitamin D 20 (2-33)
1, 25 Vitamin D 200 (6-60)
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PA is a 60 y/o man with 50 pack year history of smoking cigarettes. Presents with polyuria, constipation and confusion.

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Calcium 15.5
P 2.6
Intact PTH 4.0 (10-55)
1, 25 Vitamin D 5.0 (6-60)
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Severe Hypercalcemia (>13.5)
- Most common etiology is malignancy
- Treat even if symptoms are absent
- Aggressive treatment except in a terminally ill patient

Multiple Endocrine Neoplasia
- MEN 1
  - Primary hyperparathyroidism
  - Pancreatic Tumors
  - Pituitary Tumors
- MEN 2A
  - Medullary thyroid cancer
  - Pheochromocytoma
  - Hyperparathyroidism
Conclusion

- It is important to distinguish parathyroid from non-parathyroid hypercalcemia
- Treatment is based on severity of hypercalcemia, presence or absence of symptoms and underlying disease

Gerald D. Aurbach (1927-1991)

We learned from your wisdom, scientific acumen, investigative skills, and daring insights.