Drug Therapy for Gout

Jean D. Deupree, Ph.D.
3014 DRC
559-4565
JDDEUPRE@UNMC.EDU
http://info.unmc.edu/deupree/

Lecture Objectives

- Acute attack
  - Pharmacological treatment
  - Prophylactic measures
- Prophylactic treatment of hyperuricemia
  - Causes
  - Pharmacological treatment
  - Therapeutic complications

Hyperuricemia

- Biochemical definition:
  - Serum uric acid plasma levels above 7 mg %
  - Serum is supersaturated with uric acid
- Clinical definition
  - Serum urate level that is greater than 2 S.D. above the mean value in a gender- and age-matched population
  - Usually 8.0-8.5 mg/dl
- Normal serum urate concentrations
  - 5.1 ± 1.0 mg/dl in men
  - 4.0 ± 1.0 mg/dl in women
Why Does Hyperuricemia Occur?

- **Foods High in Purines**
  - Anchovies
  - Organ meat
  - Shellfish
  - Wild game
  - Beer

![Diagram of purine metabolism and feedback control](attachment:image.png)

**Fig 2:** Sex-age specific mean serum uric acid, Tehran, 1999-2001.

- **Women (n=133)**
- **Men (n=362)**

- **Purine assembly line**
- **Ribonucleotides**
- **DNA/RNA**
- **Hypoxanthine** → **Xanthine**
- **Uric Acid**
Drugs Causing Hyperuricemia

- Cyclosporine
- Cytotoxic agents
- Diuretics
- Ethambutol
- Ethanol
- Nicotinic acid
- Pyrazinamide
- Salicylates (low doses)

Why Do You Want to Treat Hyperuricemia?

- To prevent recurrence of acute attacks of gout
- To prevent tophaceous deposits from occurring
- To allow tophaceous deposits to dissolve
- To prevent deposition of urate crystals in the kidney

When Do You Treat Hyperuricemia?

- If symptoms of gout develop
- If there is a family history of gout
- If nephrolithiasis or renal failure are present
- If there is excretion of > 1.1 gm uric acid/day
- If plasma uric acid levels are > than
  - 10 mg/dl in females
  - 13 mg/dl in males

Drugs Which Can Be Used to Treat Hyperuricemia

- Uricostatic Drugs
  - ALLOPURINOL (Zyloprim)
- Uricosuric Drugs
  - PROBENECID (Benemid)
  - Sulfinpyrazone (Anturane)
Mechanism of Action: Allopurinol

Allopurinol

Xanthine Oxidase

Oxypurinol

Xanthine Oxidase

Hypoxanthine

Inhibits

Inhibits

Xanthine Oxidase

Uric Acid

Mechanism of Action: Allopurinol

Pharmacokinetics: Allopurinol

- Metabolized to oxypurinol
- Half-life
  - Allopurinol = 1.3 hrs
  - Oxypurinol = 21 hrs
- Oxypurinol excreted in urine

Adverse Effects: Allopurinol

- Common side effects
  - GI irritation
  - Headache
  - Skin rash
- Rare side effects
  - Drowsiness, metallic taste
  - Allopurinol hypersensitivity syndrome
    - Rash and pruritis
    - GI distress
    - Fever
    - Hepatic and renal dysfunction

Drug - Drug Interactions: Allopurinol

- Inhibition of cytochrome P450 enzymes
  - Oral hypoglycemic agents
  - Anticoagulants
- Inhibits metabolism of
  - Mercaptopurine
  - Azathioprine
- Increases toxicity of cyclophosphamide

Uses: Allopurinol

- Primary hyperuricemia
- Secondary hyperuricemia
- To inhibit perfusion injury of tissues to be transplanted
Therapeutic Problems: Allopurinol

- Slow decrease in serum uric acid levels
- Slow dissolution of tophaceous deposits

Therapeutic Problems: Allopurinol

- Slow decrease in serum uric acid levels
- Slow dissolution of tophaceous deposits
- Increased incidence of acute attacks of gout

Requirements for an Acute Attack of Gout to Occur

- Presence of uric acid crystals in joint
- Phagocytosis of uric acid crystals by granulocytes
Why Do Acute Attacks of Gout Occur When You Start to Treat Hyperuricemia?

- As the plasma uric acid levels drop, uric acid crystals in the tophaceous deposits start to dissolve
- Uric acid crystals break off and enter the synovial fluid
- Phagocytosis of uric acid crystals by neutrophils
Therapeutic Problems: Allopurinol

- Slow decrease in serum uric acid levels
- Slow dissolution of tophaceous deposits
- Increased incidence of acute attacks of gout
  - Use colchicine prophylactically to prevent acute attacks

Uricosuric Agents

- PROBENECID (Benemid)
- Sulfinpyrazone (Anturane)
- ASPIRIN (High doses 10-17 tablets/day, 4-6 gm)

Urinary Excretion of Uric Acid

Low Dose Uricosuric Therapy

Low dose aspirin
**Full Therapeutic Dose: Uricosuric**

- High dose aspirin 4 - 6 gm/day

**Effects of Aspirin on Uric Acid Excretion**

- Low doses (two aspirin tablets):
  - Blocks active transport of uric acid into the renal tubule
  - **Produces hyperuricemia**
- High doses (4-6 gm, 10-17 tablets):
  - Blocks active transport of uric acid into the renal tubule
  - Block active transport of uric acid from the renal tubule back into the peritubular fluid
  - **Uricosuric effect**

**Pharmacokinetics: PROBENECID**

- No significant problems
- Shorter half-life than allopurinol/oxypurinol

**Therapeutic Problems: Uricosuric Agents**

- Uric acid crystal formation in nephron
- Prevent formation of renal lithiasis by
  - Starting with 1/4 to 1/2 normal dose
Therapeutic Problems: Uricosuric Agents

- Uric acid crystal formation in nephron
- Prevent formation of renal lithiasis by
  - Starting with 1/4 to 1/2 normal dose
  - Making urine alkaline
    - Sodium bicarbonate
    - Potassium citrate
  - Increasing fluid intake
    - 2 – 3 liters/day

Therapeutic Problems: Uricosuric Agents

- Contraindications
  - Frequent renal lithiasis
  - Excretion of > 800 mg uric acid/day
  - Renal function impairment
    - Glomerular filtration rates of <50 ml/min

Therapeutic Problems: Uricosuric Agents

- Slowly decreasing plasma uric acid levels
- Increased incidence of acute attacks of gout

Drug-Drug Interactions: Probenecid

- ↓ Secretion of some acidic organic drugs
- + Aspirin (and some NSAIDS) → ↓ uricosuric effect
- Can be given with ALLOPURINOL
  - Adjust the dose
    - Probenecid speeds up excretion of oxypurinol
    - Allopurinol increases $t_{1/2}$ of probenecid
  - ↓ Metabolism of naproxen

Adverse Effects: Probenecid

- Most common
  - GI distress
  - Renal lithiasis
- Minor effects
  - Hypersensitivity
  - Headache
  - Urinary frequency
  - Hemolytic anemia
  - Dizziness
  - Flushing

Drug of Choice: Hyperuricemia

- First drug of choice: uricosuric agents
- Allopurinol drug of choice when
  - Uric acid excretion > 800 mg/day
  - Renal insufficiency
  - Nephrolithiasis
  - Large tophi
  - Cytotoxic therapy for myeloproliferative diseases
Causes of Acute Attacks
- Rapid fluctuations in plasma uric acid levels caused by
  - Dietary stress
  - Physical stress
  - Drugs which cause hyperuricemia

Pharmacological Therapy: Acute Attack of Gout
- First choice drugs
  - INDOMETHACIN
  - NSAIDs
- Second choice drug
  - COLCHICINE
- Last resort
  - Corticosteroids
    - Intra-articular
    - Systemic (tapered)

Mechanism of Action: Colchicine
- Prevents formation of microtubules
- Inhibits migration of leukocytes
Review

• Prophylactic treatment of hyperuricemia
  – Allopurinol
  – Probenecid
• Treatment of acute attack of gout
  – #1: Indomethacin
  – #2: Colchicine
  – #3: Coricosteroids

Colchicine

• Inhibits the formation of microtubules
  – Migration of leukocytes
  – Phagocytosis of uric acid crystals
  – Blocks cellular mitosis at toxic doses

Questions

• What effect does colchicine have on
  – Decreasing the pain and inflammation that is already present?
  – Acute attack that has been in progress for 24 hours?
  – Other types of inflammatory reaction?
  – Hyperuricemia?
  – Tophaceous deposits?

Modes of Administration of Colchicine

• Oral
  – Very irritating to the GI tract
    • Sever vomiting and diarrhea
    • GI side effects occur at about the same dose that produces therapeutic effects
• IV (preferred route)
  – May cause local tissue damage

Colchicine Treatment Schedule

• Give one tablet orally every hour until
  – Therapeutic effect is seen
  – Or there is evidence of GI side effects
  – Limit the total intake 4 - 10 mg (usually 6 mg)
• Give two tablets every two hour as above
• Give 3 mg IV over a 10-20 min period
Other Therapeutic Considerations: Colchicine

- Sooner the drug is given the more beneficial
- Full dose of colchicine should not be repeated until two weeks have elapsed
- Use with caution when liver and/or kidney disease is present

Pharmacokinetics: Colchicine

- Elimination
  - Metabolism (partial)
  - Fecal excretion
  - Urinary excretion -- 28%
- Present in leukocytes 9 days after iv administration

Therapeutic Uses: Colchicine

- Diagnostic aid for gout
  - 75 - 90% gout cases will respond
  - 5 % other arthritic conditions will respond
- Treat acute attack of gout
- Prophylactically to prevent recurring attacks
  - 1 - 3 tablets/day
  - Tolerance does not develop

Adverse Effects: Colchicine

- Initial signs associated with toxicity
  - Burning throat
  - Abdominal pain
  - Diarrhea
  - Nausea
  - Vomiting
  - Hemorrhagic colitis

- Toxic effects
  - Anuria
  - Alopecia
  - Bone marrow suppression
  - Hepatocellular failure
  - Seizures
  - Arrhythmias leading to complete heart block
  - Death
- Treatment of toxic overdose
  - Colchicine-specific Fab antibody fragments
- Additional side effects
  - Tissue necrosis at the site of injection
  - Hypersensitivity reactions
Additional References


Review

- Table at end of handout
- Review will be posted
- PowerPoint presentation and practice exam questions – http://info.unmc.edu/deupree/