Chapter 8

Xanthines
Clinical Indications for Use of Xanthines

- Use in asthma
  - Theophylline: maintenance therapy (step 2 or higher) of mild, persistent asthma
  - Side effects and narrow therapeutic index may make it a poor choice versus other agents
Clinical Indications for Use of Xanthines (cont’d)

- **Use in COPD**
  - Theophylline: recommended by GOLD as alternative to $\beta_2$ agonist and anticholinergics

- **Use in apnea of prematurity**
  - First-line treatment
  - Theophylline most often used, but caffeine citrate may be better choice (safer, higher therapeutic index)
Specific Xanthine Agents

- **a.k.a. methylxanthines**
- Found as alkaloids in plant species
- Theophylline
  - Tea leaves
- Theobromine
  - Cocoa seeds or beans
- Caffeine
  - Coffee beans and kola nuts
  - Cocoa seeds or beans
  - Tea leaves
General Pharmacological Properties

- **Effects on humans**
  - CNS stimulation
  - Cardiac muscle stimulation
  - Diuresis
  - Bronchial, uterine, and vascular smooth muscle relaxation
    - Theophylline is generally classified as a bronchodilator
  - Peripheral and coronary vasodilation
  - Cerebral vasoconstriction
    - Used in headache remedies
General Pharmacological Properties (cont’d)

- **Structure-activity relations**
  - **Theophylline**
    - Methyl attachments at N-1 and N-3 enhance bronchodilation/increase side effects
  - **Caffeine**
    - Additional methyl group at N-7 decreases bronchodilation
  - **Dyphylline**
    - Derivative of theophylline with methyl attachment at N-7 that weakens bronchodilation
  - **Enprophylline**
    - Not available in United States
    - Potent bronchodilator
    - Large substitution at N-3 position
General Pharmacological Properties (cont’d)

- Proposed theories of activity
  - Exact mechanism of action unknown
    - Smooth muscle relaxation via inhibition of phosphodiesterase (?)
    - Antagonism of adenosine (?)
    - Catecholamine release (?)
Titrating Theophylline Doses

- Individuals metabolize theophylline at different rates
- Equivalent doses of theophylline salts
  - Anhydrous theophylline = 100% theophylline
  - Salts of theophylline not pure by weight
Titrating Theophylline Doses (cont’d)

- Serum levels of theophylline
  - <5 μg/ml: No effects seen
  - 10 to 20 μg/ml: Therapeutic range
  - >20 μg/ml: Nausea
  - >30 μg/ml: Cardiac arrhythmias
  - 40 to 45 μg/ml: Seizures

- Asthma
  - 5 to 15 μg/ml

- COPD
  - 10 to 12 μg/ml
Titrating Theophylline Doses (cont’d)

- **Dosage schedules**
  - Used to titrate drug levels
  - **Rapid theophyllization:**
    - 5 mg/kg *lean body weight* oral loading dose of anhydrous theophylline
    - Each 0.5 mg/kg = 1 μg/ml serum level
  - **Slow titration:**
    - 16 mg/kg/24 hr or 400 mg/24 hr *(whichever is less)*
Titrating Theophylline Doses (cont’d)

- Methods of titration:
- Clinical reaction of patient
- Serum drug levels
  - 1 to 2 hours after administration (immediate release)
  - 5 to 9 hours after administration (sustained release)
Theophylline Toxicity and Side Effects

- Narrow therapeutic margin
- Distressing side effects may occur at therapeutic levels
- Common side effects:
  - Gastric upset
    - Not recommended in patients with peptic ulcer or acute gastritis
  - Headache
  - Anxiety
  - Diuresis
Factors Affecting Theophylline Activity

- Conditions affecting liver/kidneys
- Interactions with other drugs
- Conditions that increase theophylline levels:
  - Viral hepatitis
  - Left ventricular failure
- Condition that decreases theophylline levels:
  - Smoking
- Additive effect:
  - $\beta$ Agonists
Clinical Uses

- Asthma
  - Use debated
  - Only after other relievers and controllers have failed

- COPD
  - If ipratropium bromide and $\beta_2$ agonist fail to provide control
Nonbronchodilating Effects of Theophylline

- Increase in force of respiratory muscle contractility
- Increase in respiratory muscle endurance
- Increase in ventilatory drive
- Cardiovascular effects
  - Increased cardiac output
  - Decreased pulmonary vascular resistance
- Antiinflammatory effects
Use in Apnea of Prematurity

- Xanthines are the first-line choice when nonpharmacological methods unsuccessful
- Caffeine citrate preferred over theophylline
  - Loading dose of 20 mg/kg
  - Daily maintenance dose of 5 mg/kg