Clinical Indications

• Theophylline
  – management of asthma and COPD
  – treatment of apnea of prematurity (AOP)
  – diuretic (obsolete use)
  – classified as a bronchodilator, but is weaker than β agonists
  – effects may be from stimulation of the ventilatory drive or direct strengthening of the diaphragm
• Caffeine
  – treatment of apnea of prematurity (AOP)

Clinical Indications

• Use in asthma
  – sustained-release theophylline is indicated as a long-term maintenance drug for mild, persistent (step 2) asthma
  – it is considered less desirable than corticosteroids or cromolyn-like drugs as a 2nd or 3rd line agent
  – NAEPP EPR II does not give preference of methylxanthines over these drugs or the anti-leukotriene agents e.g. zafirlukast (Accolate) and montelukast (Singulair), and many believe the anti-leukotriene agents are preferable
  – methylxanthines are not generally recommended for acute exacerbations if asthma is in the EPR II

Clinical Indications

• Use in COPD
  – guidelines from GOLD (Global Initiative for Chronic Obstructive Lung Disease) state that bronchodilators, including theophylline, are central to symptom management
  – GOLD also states that inhaled bronchodilators are preferred, in part because of the toxicity potential of theophylline – so theophylline is considered an alternative treatment
  – methylxanthines should be used for moderate (Stage II) and severe (Stage III) COPD
  – GOLD guidelines recommend methylxanthines by IV as an adjunct to sympathomimetics and parasympathomlytics in the treatment of COPD exacerbations

Clinical Indications

• Use in Apnea of Prematurity (AOP)
  – methylxanthines are considered the first-line treatment to stimulate breathing in AOP where pharmacological intervention is required
  – theophylline is the most commonly used agent, however recent studies show that caffeine citrate (Cafcit) may be the agent of choice - caffeine citrate has been approved for both oral and IV administration
Specific Agents

- **Methylxanthines**
  - Xanthine is a nitrogenous compound found in muscle tissue, liver, spleen, pancreas and other organs as well as in the urine - it is formed during the degradation of adenosine monophosphate.
  - The methylxanthines, so named because of their methyl attachments, are a group of naturally occurring agents present as caffeine, theophylline, and theobromine.
  - Caffeine is found in coffee beans, tea leaves, cacao seeds, and beans and kola nuts; theophylline is found in tea leaves; theobromine is found in cacao seeds and beans - all have been used through time as brews for their stimulant effects.

Specific Agents

- **Methylxanthines**
  - Theophylline is available in many brand names and in a variety of forms, including sustained-release.
  - Aminophylline (theophylline and ethylenediamine tetraacetic acid (EDTA)) is available in several oral forms and as an injectable as well - attempts to use aminophylline as an aerosol agent have been unsuccessful due to side effects.
  - Several synthetic methylxanthines are now available, including dyphylline, prophylline, and enprofylline.

General Pharmacological Properties

- **Physiological effects**
  - CNS stimulation
  - Cardiac muscle stimulation
  - Diuresis
  - Bronchial, uterine, and vascular smooth muscle relaxation
  - Peripheral and coronary vasodilation
  - Cerebral vasoconstriction

Mode of Action

- **Structure-activity relations (Fig. 8-2, p. 154)**
  - Caffeine - the additional methyl group at the nitrogen-7 position decreases its bronchodilating effect.

Mode of Action

- **Structure-activity relations (Fig. 8-2, p. 154)**
  - Theophylline - the methyl attachments at the nitrogen-1 and -3 positions enhance both the bronchodilating effects and side effects.

Mode of Action

- **Structure-activity relations (Fig. 8-2, p. 154)**
  - Dyphylline - the rather large attachment at the nitrogen-7 decreases its bronchodilating effect.
Methylxanthines

Mode of Action

• Structure-activity relations (Fig. 8-2, p. 154)
  - enprofylline - the large substitution at the nitrogen-3 position enhances its bronchodilating effect

Mode of Action

• Theories of activity
  - antagonism of adenosine
    - adenosine can stimulate A₁ and A₂ receptors - A₁ receptor stimulation inhibits cAMP; A₂ receptor stimulation increases cAMP (inhaled adenosine has caused bronchoconstriction in asthmatic patients)
    - theophylline is a potent inhibitor of adenosine and could block smooth muscle contraction mediated by A₁ receptors
      - this explanation is contradicted by the action of enprofylline, which is 5 times more potent than theophylline for bronchodilation, but does not antagonize adenosine

Mode of Action

• Theories of activity
  - inhibition of phosphodiesterase (PDE)
    - original mode of action ascribed to the methylxanthines
    - an increase in cyclic 3',5' AMP causes a relaxation of bronchial smooth muscle (β-adrenergic agents increase cAMP)
    - PDE hydrolyzes cAMP to 5' AMP thereby reducing levels of cAMP
      - methylxanthines inhibit PDE, preventing the hyrolyzing of cAMP and theoretically increasing levels of cAMP and therefore, bronchodilation
      - recent studies show that at the dosage levels used clinically, theophylline is poor inhibitor of PDE - this is no longer considered an acceptable theory of how xanthines work

Mode of Action

• Theories of activity
  - catecholamine release
    - methylxanthines may cause the release of endogenous catecholamines, causing tremor, tachycardia and bronchial smooth muscle relaxation
      - however, studies have reported conflicting results, with both an increase and no change reported

Mode of Action

• Theories of activity
  - conclusion
    - the precise mode of action of methylxanthines is unknown
      - could be any one mentioned so far
      - could be inhibition of calcium uptake by the sarcoplasmic reticulum
      - could be antagonism of prostaglandins
      - no definitive explanation exists - it will probably turn out that there are multiple mechanisms involved with the specific agents

Titrating Theophylline Doses

• Serum levels
  - in 1972 Jenne, et al determined the therapeutic serum level of theophylline to be 10-20 mcg/ml, and developed the following ranges
    - < 5 mcg/ml: no effects
    - 5-10 mcg/ml: therapeutic range
    - > 20 mcg/ml: nausea
    - > 30 mcg/ml: cardiac dysrhythmias
    - > 40-45 mcg/ml: seizures
  - since that time, a more conservative range of 5-15 mcg/ml has been adopted; ATS recommends a serum level of 10-12 mcg/ml in the management of COPD - these ranges seek maximal benefit with minimal toxicity
Titrating Theophylline Doses

- Serum levels
  - there is a dose-related response to higher serum levels, however, the response does not continue at the same rate of increase as levels rise.
  - the improvement in FEV₁ tends to flatten above a serum level of 12 mcg/ml, and the toxic effects continue to increase (Fig. 8-4, p. 156)

Dosage Schedules

- Dosages
  - because of the wide variance in metabolism and tolerance, no "standard" dose of theophylline is used.
  - there are typical starting points:
    - patients who have never received theophylline, will receive an oral loading dose of 5 mg/kg, with each 0.5 mg/kg yielding a serum level of approximately 1 mcg/ml.
    - if a patient has previously received theophylline, a serum level should first be determined.
    - subsequent dosing is guided by patient response, or better still, serum levels.
    - serum levels should be checked at the time of peak absorption – 1-2 hrs after immediate release forms and 5-9 hrs after the morning dose of sustained-release forms.

Toxicity and Side Effects

- Therapeutic margin
  - this margin is very narrow with methylxanthines.
  - distressing side effects can be seen even within the therapeutic range of 5-15 mcg/ml
  - gastric upset, headache, anxiety and nervousness are seen as less toxic effects, but can lead to loss of work or school days.
  - the diuretic effect should be monitored closely in patients with excess airway secretions to ensure adequate hydration.
  - reactions to theophylline levels can be unpredictable from patient to patient – some may show no ill effects at 20 mcg/ml, whereas some may have problems at 5 mcg/ml and some may pass directly from nausea to seizures.
  - dosing is very patient specific.

Factors Affecting Activity

- Metabolism
  - theophylline is metabolized in the liver and eliminated by the kidneys.
  - any condition affecting these systems will affect serum levels.

- Drug interactions
  - the list of drugs affecting serum levels and activity of theophylline is long and varied (Box 8-2, p. 157).
  - theophylline and the β agonists have an additive effect and are often combined in treating asthma and COPD.
  - theophylline can antagonize the benzodiazepines (Valium) and can reverse non-depolarizing neuromuscular blocking agents, e.g. pancuronium (Pavulon) and atracurium (Tracrium).

Factors Affecting Activity

- Drug interactions
  - other drugs, e.g. furosemide (Lasix) have very unpredictable effects, either increasing or decreasing theophylline levels and require frequent monitoring of serum levels.

- Other
  - cigarette smoking increases production of liver enzymes that inactivate methylxanthines and necessitates higher doses.
Clinical Application

• Recent guidelines do not indicate theophylline as a first-line therapy due to:
  – the narrow therapeutic margin
  – toxic side effects
  – unpredictable serum levels
  – the need for individual dosing
  – numerous drug-drug and drug-condition interactions

Use in asthma
  – theophylline is recommended for use after reliever agents, e.g. β-agonists, inhaled steroids and/or mediator antagonists (cromolyn) which target the underlying inflammation

Clinical Application

• Use in COPD
  – use of theophylline as a maintenance drug is indicated if ipratropium bromide (Atrovent) and a β agonist fail to provide adequate control
  – the long-acting β agonists also offer another choice and may be preferable due to the increased AUC over 12 hours
  – GOLD guidelines do list theophylline and IV aminophylline as agents for use in managing acute exacerbations of COPD
  – methylxanthines should not be used in patients with active PUD or acute gastritis due to GI side effects – administration may be tried at meal times to decrease these effects
  – ingestion of large amounts of caffeine may precipitate side effects

Non-bronchodilating effects
  – since theophylline is actually a rather weak bronchodilator, its efficacy in obstructive lung disease may be more from its effects on ventilation
  – this theory is consistent with the fact that significant clinical improvement may be present despite little improvement in expiratory flow rates
  – non-bronchodilating respiratory effects
    • increase in the force of respiratory muscle contractility
    • increase in respiratory muscle endurance and strength
    • increase in ventilatory drive at the CNS level

Clinical Application

• Non-bronchodilating effects
  – cardiovascular effects
    • increased cardiac output
    • decreased pulmonary vascular resistance
    • improved myocardial muscle perfusion
  – anti-inflammatory effects
    • inhibition of cAMP-specific PDE enzymes
    • inhibition of pro-inflammatory cytokines
    • decreased late phase response to histamine in asthmatics
    • reduced airway responsiveness to stimuli such as histamine, methacholine, allergens, adenosine
  – these effects can occur at lower serum levels (9-10 mcg/ml) than those usually recommended for bronchodilation

Use in apnea of prematurity (AOP)
  – when non-pharmacological methods are not successful in treating AOP, methylxanthines are still considered the first-line drug therapy due to their effects on respiratory muscle contractility and strength
  – although theophylline is biotransformed to caffeine in neonates, caffeine is preferred
    • caffeine penetrates into CSF more readily than theophylline and can be effective in neonates refractory to theophylline therapy
    • caffeine is a more potent stimulant of the CNS
    • caffeine dosing regimens are simpler and have more predictable results
    • caffeine has a wider therapeutic margin and fewer side effects

Clinical Application

• Use in AOP
  – a standard preparation, caffeine citrate (Cafcit), is available and can be administered orally or intravenously
  – recommended loading dose is 20 mg/kg, followed in 24-48 hrs by a single daily maintenance dose of 5 mg/kg
  – serum levels of 5-20 mg/L of caffeine have been found to be effective
Summary of Bronchodilating Agents

- **Sympathomimetic (adrenergic) agents**
  - indicated for the treatment of reversible airway obstruction in diseases such as asthma and COPD — these agents produce bronchodilation by stimulating β2 receptors on bronchial smooth muscle
  - β2 specificity is thought to be due to the side chain bulk — the keyhole theory
  - routes of administration for β2 agonists include inhaled aerosol, oral and parenteral, with the least side effects with inhaled agents
  - the catecholamines have the shortest duration due to metabolism by COMT

  - modification of the catecholamine structure produced other agents such as metaproterenol, albuterol and terbutaline which have 4-6 hr duration of action and are more β2 specific
  - further modification lead to salmeterol and formoterol, the long-acting β2 agonists with a 12 hour duration of action
  - adverse effects include tremor, headache, insomnia, tachycardia, possible bronchoconstriction with MDIs and tolerance
  - the β agonists have been questioned as a possible factor in the increase in asthma mortality, leading to the “β agonist controversy”

- **Parasympatholytic (anticholinergic) agents**
  - these agents produce bronchodilation by blocking the effect of acetylcholine at the cholinergic receptors on bronchial smooth muscle
  - the only agent approved for inhalation at this time is ipratropium bromide (Atrovent) which is indicated for treatment of airflow obstruction in COPD
  - quaternary compounds such as ipratropium are fully ionized and are less readily absorbed from the site of deposition, giving a more localized effect
  - the most common side effects are dry mouth and cough

- **Combination therapy** — anticholinergic + β2 agonist — may provide additive bronchodilating results in COPD and severe, acute asthma
Methylxanthines

- The exact mechanism by which these agents produce bronchodilation is not fully understood—several theories have been advanced, including antagonism of adenosine.
- Clinical uses include management of asthma and COPD and the treatment of apnea of prematurity in neonates.
- Because of the wide variance in metabolism and tolerance, no "standard" dose of theophylline is used and dosing must be individually titrated.
- Therapeutic serum levels are considered to be 10-12 µg/ml in COPD and 5-15 µg/ml in asthma.

- Summary of Bronchodilating Agents

- Methylxanthines
  - The therapeutic margin is very narrow and side effects include gastric upset, headache, insomnia, nervousness, palpitations, and diuresis.
  - Serum levels are affected by many variables that can either increase or decrease the amount of drug in the body.
  - In COPD, the non-bronchodilating effects, e.g., stimulation of ventilation and increased respiratory muscle function may be of benefit.
  - In treating asthma, theophylline is recommended for use after reliever agents, e.g., β agonists, inhaled steroids and/or mediator antagonists (cromolyn) which target the underlying inflammation.

- Summary of Bronchodilating Agents

- Methylxanthines
  - GOLD guidelines list theophylline and IV aminophylline as agents for use in managing acute exacerbations of COPD.
  - When treating AOP, caffeine is the preferred agent.