

RSPT 2217  
Methylxanthines

Gardenhire  
Chapter 8

### From the Text

- Key Terms and Definitions
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- Xanthine Derivatives Used as Bronchodilators
  - Table 8-1; page 152
- Adverse Reactions Seen with Theophylline
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- Factors That Can Increase or Decrease Theophylline Levels
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### 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  $\beta$  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 2<sup>nd</sup> or 3<sup>rd</sup> 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 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 parasympatholytics 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

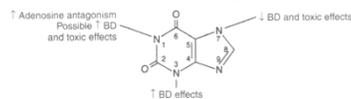
- Methylxanthines
  - theophylline is available under many brand names and in a variety of forms, including sustained-release
  - aminophylline (theophylline and ethylenediamine tetraacetic acid (EDTA)) is available in several oral forms and as an injectable as well - attempts to use aminophylline as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

### General Pharmacological Properties

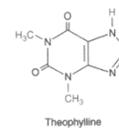
- Physiological effects
  - CNS stimulation
  - cardiac muscle stimulation
  - diuresis
  - bronchial, uterine and vascular smooth muscle relaxation
  - peripheral and coronary vasodilation
  - cerebral vasoconstriction

### Mode of Action

- Structure-activity relations (Fig. 8-2, p. 154)

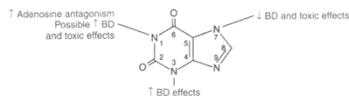


- theophylline - the methyl attachments at the nitrogen-1 and -3 positions enhance both the bronchodilating effects and side effects

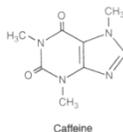


### Mode of Action

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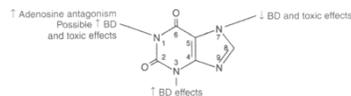


- caffeine - the additional methyl group at the nitrogen-7 position decreases its bronchodilating effect

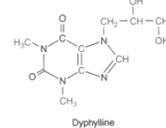


### Mode of Action

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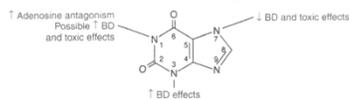


- dyphylline - the rather large attachment at the nitrogen-7 decreases its bronchodilating effect

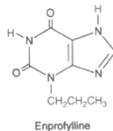


### Mode of Action

- 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
  - 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 ( $\beta$ -adrenergic agents increase cAMP)
    - PDE hydrolyzes cAMP to 5' AMP thereby reducing levels of cAMP
    - methylxanthines inhibit PDE, preventing the hydrolyzing 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
  - antagonism of adenosine
    - adenosine can stimulate  $A_1$  and  $A_2$  receptors -  $A_1$  receptor stimulation inhibits cAMP;  $A_2$  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  $A_1$  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
  - 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

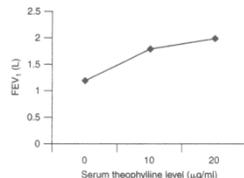
- Theories of activity
  - conclusion
    - the precise mode of action of methylxanthines is unknown
    - could be any one mentioned so far
    - could be inhibition of calcium uptake by the sarcoplasmic reticulum
    - could be antagonism of prostaglandins
    - no definitive explanation exists - it 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
    - 10-20 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

### Titration 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 FEV<sub>1</sub> 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

### Toxicity and Side Effects

- CNS
  - headache
  - anxiety
  - restlessness
  - insomnia
  - tremor
  - convulsions
- GI
  - nausea, vomiting
  - anorexia
  - abdominal pain
  - diarrhea
  - hematemesis
  - GI reflux
- Respiratory
  - tachypnea
- Cardiovascular
  - palpitations
  - supraventricular tachycardia
  - ventricular dysrhythmias
  - hypotension
- Renal
  - diuresis

### 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  $\beta$  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.  $\beta$  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  $\beta$  agonist fail to provide adequate control
  - the long-acting  $\beta$  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

### Clinical Application

- 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

### Clinical Application

- 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 apnea of prematurity (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

### From the Text

- Self-Assessment Questions
  - page 159
- Clinical Scenario
  - page 160

### Summary of Bronchodilating Agents

### 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  $\beta_2$  receptors on bronchial smooth muscle
  - $\beta_2$  specificity is thought to be due to the side chain bulk – the keyhole theory
  - routes of administration for  $\beta$  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

### Summary of Bronchodilating Agents

- Sympathomimetic (adrenergic) agents
  - 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  $\beta_2$  specific
  - further modification lead to salmeterol and formoterol, the long-acting  $\beta_2$  agonists with a 12 hour duration of action
  - adverse effects include tremor, headache, insomnia, tachycardia, possible bronchoconstriction with MDIs and tolerance
  - the  $\beta$  agonists have been questioned as a possible factor in the increase in asthma mortality, leading to the “ $\beta$  agonist controversy”

### Summary of Bronchodilating Agents

- 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

### Summary of Bronchodilating Agents

- Parasympatholytic (anticholinergic) agents
  - some patients with COPD show greater reversibility of airflow obstruction with an anticholinergic than with a  $\beta$  agonist
  - combination therapy – anticholinergic +  $\beta$  agonist – may provide additive bronchodilating results in COPD and severe, acute asthma

### Summary of Bronchodilating Agents

- 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

