RSPT 2317
Anticholinergic Bronchodilators
(Parasympatholytics)

Gardenhire
Chapter 7

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History & Development

- Prototypical parasympatholytic agent is atropine
  - an alkaloid found naturally in the plants *Atropa belladona* (nightshade) and *Datura* species
  - scopalamine is also extracted from the belladonna - both atropine and scopalamine are known as belladonna alkaloids
  - evidence that these compounds have been ingested for thousands of years for their CNS effects
    - fumes from the burning Datura species were inhaled as treatment for respiratory disorders as early as the 17th century
  - use of Datura to treat asthma and cough reached Britain in 1802
    - in mid-19th century America, smoking Datura was a common treatment - various cigars, cigarettes and pipes were available
    - this practice was attacked on several levels, from inconsistent dosing to irritant effects

History & Development

- by the 1930s, adrenaline and ephedrine had replaced the belladonna alkaloids
- interest in parasympatholytics was renewed in the 1980s
  - new understanding of their role
  - introduction of atropine derivatives with fewer side effects
- ipratropium bromide was released in the U.S. in 1987 as Atrovent
- a new, long-acting anticholinergic bronchodilator (24 hour action following a single dose), tiotropium is under investigation

Clinical Indications

- Anticholinergic bronchodilators
  - ipratropium and other anticholinergic agents are indicated for maintenance treatment in asthma and COPD, including chronic bronchitis and emphysema
- Combined anticholinergic and sympathomimetics bronchodilators
  - e.g. Combivent - indicated for patients with COPD on regular treatments who require additional bronchodilation relief of airflow obstruction
  - ipratropium is also used in conjunction with sympathomimetics in severe asthma, especially during acute episodes that do not respond to β agonist therapy

Anticholinergic bronchodilators

- Anticholinergic nasal spray
  - indicated for symptomatic relief of allergic and non-allergic perennial rhinitis and the common cold

Specific Agents

- Atropine sulfate
  - a tertiary ammonium compound that is not fully ionized and is readily absorbed from the GI tract and respiratory mucosa
  - bronchodilation and side effects are both dose-related
    - children - 0.05 mg/kg tid-qid
    - adults - 0.025 mg/kg tid-qid
    - greater bronchodilation and duration of action are seen at dosages of 0.05-0.1 mg/kg
      - side effects (dry mouth, blurred vision, tachycardia) at this dosage schedule are unacceptable

Specific Agents

- Ipratropium bromide (Atrovent)
  - a quaternary ammonium derivative of atropine that is fully ionized and does not distribute well across lipid membranes, so its distribution is limited more to the lung when inhaled
  - available as
    - an MDI delivering 18 mcg/puff
    - a nebulizer solution of 0.02% concentration in a 2.5 ml vial, delivering a 500 mcg dose per treatment
    - a nasal spray solution of 0.03% delivering 21 mcg/spray
    - a nasal spray solution of 0.06% delivering 42 mcg/spray

Specific Agents

- Ipratropium bromide (Atrovent)
  - ipratropium bromide is poorly absorbed into the circulation from both the nasal mucosa when given by nasal spray and from the airway when inhaled
  - the clinical effect profile differs from β adrenergic agents in that bronchodilation begins within minutes, but proceeds more slowly to a peak effect in 1-2 hours
  - in asthma, the duration of action is similar to β adrenergic agents, however, in COPD the duration is longer by 1-2 hours

Specific Agents

- Ipratropium and albuterol (Combivent)
  - a combination MDI product
    - ipratropium 18 mcg/puff
    - albuterol 90 mcg/puff
  - product has been shown to be more effective in stable COPD than either product alone

  (a combination product of ipratropium (0.04 mg/puff) and fenoterol (0.1 mg/puff) is available as Duovent in Great Britain)

Specific Agents

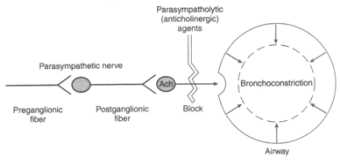
- Tiotropium bromide (Spiriva)
  - developed as a long-acting bronchodilator
  - structurally related to ipratropium and is poorly absorbed after inhalation
  - appears to maintain a higher level of baseline bronchodilation than ipratropium
  - dosage is 18 mcg inhaled once daily from the DPI (HandiHaler), which provides significant bronchodilation for 24 hours

Mode of Action

- Bronchomotor tone
  - in the normal airway, a basal level of bronchomotor tone is caused by parasympathetic activity
  - this basal level can be abolished by the administration of atropine, suggesting it is mediated by acetylcholine
  - administration of a parasympathomimetic agent e.g. methacholine can intensify the level of bronchial tone to the point of constriction in healthy subjects and more so in asthmatics (methacholine challenge)

Mode of Action

- Bronchomotor tone
  - anticholinergic (parasympatholytic) agents e.g. atropine, ipratropium and tiotropium competitively block the action of acetylcholine and can block cholinergic-induced bronchoconstriction
  - atropine has been shown to inhibit exercise-induced asthma, psychogenic bronchoconstriction and bronchoconstriction caused by β blockade



Adverse Effects

- MDI & SVN (common)
  - dry mouth
  - cough
- MDI (occasional)
  - nervousness
  - irritation
  - dizziness
  - headache
  - palpitation
  - rash
- SVN
  - pharyngitis
  - dyspnea
  - flu-like symptoms
  - bronchitis
  - upper respiratory infections
  - nausea
  - occasional bronchoconstriction
  - eye pain
  - urinary retention (<3%)

Clinical Application

- Use in COPD
  - have been found to be more potent bronchodilators than β adrenergic agents in bronchitis-emphysema
    - this will likely be their primary clinical application
  - tiotropium offers a prolonged duration of action of up to 24 hrs with a single, daily inhalation
- Use in asthma
  - not even labeled for asthma use in U.S.
    - indicated as a bronchodilator for maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema
  - while they have been proven more effective in COPD and bronchitis, they have not been proven superior to treat asthma

Clinical Application

- Use in asthma
  - may be especially useful in the following applications:
    - nocturnal asthma, where the longer duration may protect against night-time deterioration of flows
    - psychogenic asthma which may be mediated through vagal parasympathetic action
    - asthmatic patients who require β blocking agents
    - as an alternative to theophylline in patients with notable side effects from that drug
    - acute, severe episodes of asthma, not responding to β agonists

Clinical Application

- Combination therapy in COPD
  - should offer advantages in treating COPD based on
    - complementary sites of action: anticholinergic acting on the more central airways and β agonist acting on smaller, more peripheral airways
    - mechanisms of action of anticholinergic and β agonist agents are separate and complementary
  - additive effect
    - a 1996 study of 462 patients in 25 medical centers over 85 days showed superior efficacy of combination therapy as compared to either class of drug given alone

Clinical Application

- Combination therapy in COPD
  - sequence of administration
    - this has been argued both ways
      - parasympatholytic first since it acts in the larger airways
      - sympathomimetic first since it has a more rapid onset of action and it acts in both large and small airways
      - no strong data support either method
      - according to Rau, sequence probably doesn't matter and preparations such as Combivent and the mixing of albuterol and Atrovent make it a moot point

Assessment of Anticholinergic Therapy

- Assess the effectiveness of therapy based on the indication(s) for the aerosol agent
  - presence of reversible airflow obstruction resulting from primary bronchospasm or obstruction 2° to inflammation or secretions, either acute or chronic
- Monitor flow rates with a bedside peak flow meter, portable spirometry or lab reports of pulmonary function
  - pre- and post-bronchodilator studies may not predict response to parasympatholytics, since β adrenergics are used for those tests
- Perform respiratory assessment before and after treatment
- Assess pulse before, during and after treatment

Assessment of Anticholinergic Therapy

- Assess patient's subjective reaction to therapy
- Assess ABGs or SpO_2 as needed to monitor changes in ventilation and oxygenation
- Long term: monitor PF studies
- Instruct and verify correct use of aerosol devices
  - emphasize protection of the eye from aerosols

For long-acting parasympatholytics
  - assess ongoing lung function
  - assess amount of concomitant β agonist use and nocturnal symptoms
  - assess number of exacerbations
  - assess days of absence due to symptoms

Dosing Schedules

Anticholinergic Agents			
	Ipratropium Br	Atrovent, Atrovent HFA	SVN: 2.5 ml of 0.02% strength (500 mcg), tid, qid CFC MDI: 2 puffs, 18 µg/puff, qid HFA MDI: 2 puffs, 17 µg/puff, qid
	Ipratropium and albuterol	Combivent	MDI: 2 puffs, 18 µg/puff of ipratropium with 90 µg/puff of albuterol
		DuoNeb	SVN: ipratropium 0.5 mg and albuterol sulfate 3 mg (equal to 2.5 mg albuterol base)
	Tiotropium Br	Spiriva	DPI: 18 µg/inhalation, 1 inhalation q day