Pharmacology of the Respiratory Tract: COPD and Steroids

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Aims of Lecture

Be able to define the lung alveolar Structure (respiratory airways)

Explain the pathological changes that occur in COPD lungs (emphysema) and how it affects irreversible changes in lung function

Mechanism of action of steroids for treatment in COPD

Effect of inhaler type on steroid clinical effects in COPD
The Lung Structure

Conducting zone

Respiratory zone

Respiratory airways

Conducting airways

1. Trachea
2. Bronchi
3. Bronchioles
4. Terminal bronchioles
5. Transitional bronchioles
6. Respiratory bronchioles
7. Alveolar ducts
8. Alveolar sacs
Lung parenchyma

TB = Terminal Bronchiole
RB = Respiratory Bronchiole
AD: Alveolar Duct
Lung parenchyma

TB = Terminal Bronchiole
RB = Respiratory Bronchiole
AD: Alveolar Duct
Blood - Gas Barrier structure

Alveolar Duct

Alveoli
Epidemiology of Chronic Obstructive Pulmonary Disease (COPD)

- Defined as a chronic, progressive inflammatory lung disease characterized by airflow limitation that is not fully reversible.
- Symptoms include; shortness of breath, cough and sputum production.
- 30-40% of smokers develop COPD.
- COPD is the 4th leading cause of death in the western world (2.74 million people).
- Only leading cause of death that is increasing in prevalence worldwide.
- Disease cost in 2002, $32.1 billion.
Risk factors associated with COPD

- Smoking
  - 30-40% of smokers actually develop COPD

- Genetics
  - COPD tends to occur in families
  - 1% of COPD patients have $\alpha_1$-antitrypsin deficiency
  - Smoking Cessation – Nicotinic receptor expression

- Environmental
  - Exposure to occupational dust, gases, fumes and air pollution
  - Passive smoking - Children and adults

- Lung Infections
  - Amplify inflammatory responses and increase resistance to steroid therapy
Risk factors associated with COPD
Diagnosis of disease severity

- **GOLD guidelines for COPD diagnosis** $\text{FEV1/FVC} < 0.7$

<table>
<thead>
<tr>
<th>GOLD 1</th>
<th>Mild</th>
<th>Mild airflow limitation $\text{FEV1} \geq 80%$ predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOLD 2</td>
<td>Moderate</td>
<td>Worsening airflow limitation $50% \geq \text{FEV1} &lt; 80%$ predicted</td>
</tr>
<tr>
<td>GOLD 3</td>
<td>Severe</td>
<td>Further worsening airflow limitation $30% \geq \text{FEV1} &lt; 50%$ predicted</td>
</tr>
<tr>
<td>GOLD 4</td>
<td>Very Severe</td>
<td>Severe airflow limitation $\text{FEV1} &lt; 30%$ predicted</td>
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How can smoking be good??

Before

After
Chronic Bronchitis

- Occurs in all smokers
- Goblet cell hyperplasia and hypertrophy

Normal bronchus: Mucus gland < 40% of thickness

Chronic Bronchitis: Mucus gland > 40% of thickness

Excess secretions of mucus
Emphysema

- Defined as irreversible destruction of gas-exchange surface area

Normal lung architecture

Centrilobular emphysema
- Proximal portion of terminal bronchiole is affected
- Most commonly associated with smoking

Panacinar emphysema
- Entire respiratory bronchiole affected
- α1-AT deficiency
Emphysema - Histology

- Alveolar and capillary wall destruction in emphysema through degradation of extracellular matrix (collagen and elastin)
- Decreased surface area
- Uncoupling of ventilation and perfusion leading to reduced lung function
COPD Disease mechanisms: Chronic inflammation

- Continual cigarette smoke insult results in a chronic inflammatory and oxidative process in the airways of COPD patients

- **Neutrophils** – are recruited following smoke exposure
  - Granules contain proteinases, antimicrobial agents and myeloperoxidase

- **Macrophages** – are elevated in the lungs of COPD patients
  - Release pro-inflammatory cytokines (TNFα), proteases, Reactive Oxygen Species, and mucus gland activators

- **T-Lymphocytes** – are elevated in the lungs of COPD patients
  - Release pro-inflammatory mediators
COPD Disease Mechanisms: Protease / Antiprotease imbalance

- α1-Antitrypsin deficiency
- Serine protease inhibitor
- Innate inhibitor of neutrophil elastase
- Imbalance of proteases leads to tissue destruction
COPD Disease Mechanisms: Oxidant / Antioxidant Balance

- Smoking alters the protease and oxidant balance within the lung
- Oxidation of anti-proteases leads to inactivation
- Increased inflammatory cell recruitment increases protease burden
Principles of COPD therapy

- **Smoking cessation**
  - Target therapy with buropion (antidepressant) and nicotine replacement therapy

- **Corticosteroids**
  - Reduce inflammation in the lungs of COPD patients to treat symptoms getting worse
  - Once lung function is lost it can not be replaced!

- **Oral corticosteroids (Budesonide)**
  - short-term use Side effects: Weight gain and fluid retention, Mood changes, Increased blood sugar level (type II diabetes), more lung infections.
  - long-term use Side effects: Osteoperosis, recurrent infections, stomach ulcers.

- **Inhaled steroids (Fluticasone)**
  - Side effects: Sore mouth or throat, voice changes, such as hoarseness.
Corticosteroids

Corticosteroid binds GC receptor complex which:

1) Up-regulate anti-Inflammatory proteins **TRANS-ACTIVATION**
2) Prevent translocation of inflammatory transcription factors from cytosol into nucleus **TRANSREPRESSION**

![Diagram of GC receptor complex with trans-activation and trans-repression pathways]
Corticosteroids

- Formulation is important in pulmonary deposition
  - Inhaled drug particle size
  - Aerosol vehicle
  - Inhaler technique

- Proper pulmonary deposition impacts efficacy and safety

<table>
<thead>
<tr>
<th>Particle Size</th>
<th>Location of Deposition</th>
<th>Efficacy</th>
<th>Safety</th>
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<tbody>
<tr>
<td>&gt;5 μm</td>
<td>Mouth/esophageal region</td>
<td>No clinical effect</td>
<td>Absorption from GI tract if swallowed</td>
</tr>
<tr>
<td>2–5 μm</td>
<td>Upper/central airways</td>
<td>Clinical effect</td>
<td>Subsequent absorption from lung</td>
</tr>
<tr>
<td>&lt;1 μm</td>
<td>Peripheral airways/alveoli</td>
<td>Clinical effect</td>
<td>Subsequent absorption from lung</td>
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Particle size of corticosteroids depends on inhalation medium used.
Formulation: Pulmonary Deposition

1) Higher pulmonary deposition with hydrofluoroalkane aerosol formulations

2) Reduced oropharyngeal deposition with hydrofluoroalkane aerosol formulations reduces systemic side effects