

Lecture (30)

Pharmacology of antitussive drugs and mucoactive agents

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Introduction

Acute cough is usually due to the common cold. It is the most common symptom for which patients seek medical care. An acute cough following an upper respiratory tract infection is usually **self-limiting**, but can be difficult to control and can be associated with impaired quality of life.

In the majority of patients, acute cough is caused by upper respiratory tract infections, acute bronchitis or tracheo-bronchitis due to bacterial or, more frequently, viral infections. Cough is treated symptomatically either through non-pharmacological or pharmacological interventions.

The airway mucosa responds to infection and inflammation in a variety of ways. This response often includes surface mucous (**goblet**) cell and sub-mucosal gland **hyperplasia** and **hypertrophy**, with mucus hyper-secretion.

Products of inflammation, including neutrophil-derived (DNA) and filamentous actin (F-actin), bacteria, and cell debris all contribute to mucus purulence. Expectored mucus is called sputum. Mucus is usually cleared by ciliary movement, and sputum is cleared by cough.

The general term for medications that are meant to affect mucus properties and promote secretion clearance is “mucoactive.” These include **expectorants**, **mucolytics**, **mucoregulatory**, and **mucokinetic** drugs. Mucoactive medications are intended either to increase the ability to expectorate sputum or to decrease mucus hyper-secretion.

Types of cough:

1. Use cough or productive cough (associated with sputum): it is treated by **muco-active agents** (expectorants, mucolytics, etc).

2. Useless cough or dry, non-productive cough: it is not associated with sputum and treated by **antitussive**.

N.B: Untreated chronic cough could cause many problems like piles, uterine prolapse, hernia, etc.

1-Antitussives

Antitussives are drugs which decrease the frequency and severity of non-productive cough without impairing mucociliary defenses.

Classification:

1-Narcotic antitussives.

2- Non narcotic centrally acting antitussives.

3-Peripheral antitussives.

4-Antihistamines.

1-Narcotic antitussives.

Examples:

1. Codeine
 2. Hydrocodone
 3. Morphine
- They act on opioid receptors and inhibit cough center.
 - These drugs are potent analgesics.
 - They cause euphoria and may cause dependence and addiction.
 - Respiratory center depression is the major side effect of these agents.
 - These agents are used in severe dry cough.

2- Non narcotic centrally acting antitussives. Examples:

1. Noscapine
2. Dextromethorphan
3. Benzonatate

Characters:

- Have no analgesic effect
- Less dependence
- No euphoria
- No respiratory center depression.

Dextromethorphan

- It is a Synthetic codeine analog.
- It acts through antagonizing NMDA glutamate receptors.
- It Has mild opioid effect when used in excess doses.
- Naloxone (opioid antagonist) can be given for overdose of dextromethorphan.
- Mild abuse potential.
- Dextromethorphan appears to have little serious toxicity. It is more safe than codeine.

Benzonatate

it inhibits cough center and inhibit pulmonary stretch receptors.

3-Peripheral antitussives.

Examples:

1. Inhaled local anesthetics.
2. Mucokinetics (Drugs that facilitate the removal of secretions from the respiratory tract by stimulating ciliary action like bronchodilators).

4-Antihistamines

- Antihistamines are added to many cough and cold remedies as both antitussives and to treat rhinorrhea and nasal congestion.
- Although some antihistamines may have an antitussive action, their clinical efficacy has not been well documented.
- The anticholinergic (atropine-like) action of antihistamines frequently causes a drying sensation in the throat and nasal passages and may result in thickening of bronchial secretions.

Uses of Antitussives/cough suppressants

1- Central antitussive agents can be useful in patients with **chronic bronchitis**, but have little efficacy in patients with cough due to upper respiratory infections.

2- Use of these drugs is most appropriate in specific therapy such as patients with **inoperable lung cancer**.

3- Used in cases in which an unproductive **cough interferes with sleep** or causes exhaustion.

NB: use of cough suppressants in children under six years of age should be avoided due to its safety profile.

Cough mixtures

Cough mixtures may be a combination of different active ingredients. These active pharmaceutical ingredients can be one of the following pharmacological classes: antitussives, antihistamines and mucoactive agents (mucolytic, expectorants, and mucokinetics).

Muco-active agents

1-Expectorants: Drugs which increase the volume and fluidity or hydration of airway secretions. Agents with expectorant properties as **ammonium chloride** & **guaniphesin** are often included in cough mixtures.

Guaniphesin acts through Increase the volume of watery airway secretions. This serves to thin out respiratory secretions, making them easier to cough up.

2-Mucolytics: agents which degrade polymers in secretion.

A- N-Acetyl Cysteine: disrupts disulfide bond within the mucus glycoproteins making mucus more thin and easy to be expelled.

B- Dornase alfa (DNase) clears leukocytic debris through hydrolysis of DNA polymers.

C- Bromhexine: it loosens and thins bronchial secretions by reducing surface tension and viscosity of mucus.

D- Ambroxol: Ambroxol has been thought to **stimulate surfactant secretion**, and has been used for many years in Europe (but not in USA and Canada) for the management of **chronic bronchitis** as mucolytic.

The results of clinical studies of ambroxol are conflicted; some found clinical benefit, whereas others found no benefit.

Uses of mucolytics:

1. Increases clearance of respiratory secretions (eg, common cold, pneumonia, COPD).
2. N-acetylcysteine and DNase are used in cystic fibrosis patients.
3. N-acetylcysteine is also used as an antidote for acetaminophen overdose.

Side effects of mucolytics:

- 1)-GIT irritation (when given orally oral).
- 2)-Burning sensation in airways (when given by inhalation).
- 3)-Bronchospasm (when given by inhalation).

4) Allergic reactions.

3- Mucokinetic agents: Examples:

1. Beta2 adrenergic agonists (e.g. salbutamol).
2. Methylxanthines (e.g. aminophylline).

They are bronchodilators and increase ciliary movements.