MED438
KING SAUD UNIVERSITY

pharmacology
Team 438

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Treatment of Acute and Chronic Rhinitis and Cough

- Red : important
- Black : in male / female slides
- Pink : in female's slides only
- Blue : in male's slides only
- Females doctor notes
- Grey: Males doctor notes/ extra explanations

OBJECTIVES:

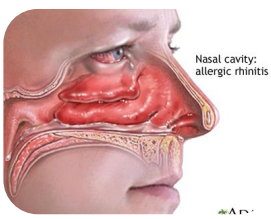
- ✓ Define rhinitis and cough.
- ✓ Classify drugs used in the treatment of rhinitis.
- ✓ Expand on the pharmacology of different drug groups used in the treatment as; antihistamines, leukotriene antagonists, corticosteroids, decongestants and anticholinergics.
- ✓ Describe the pharmacology of different expectorants and mucolytics used in the treatment of productive cough.
- ✓ Describe the pharmacology of antitussives (cough suppressants)

Editing File

Rhinitis

Definition

Rhinitis is the irritation and/or inflammation of the mucous membrane Inside the nose



Can be

Acute

Persist 7-14 days

Chronic

Persist more than 6 weeks

Types

Allergic :

seasonal; hay fever and perennial (persistent)

Infectious :

infection with bacteria,fungi & viruses

Signs & Symptoms of Rhinitis:

- Rhinorrhea "Runny nose"
- Sneezing
- Nasal congestion
- Post nasal drip
- Systemic effect "fever, body aches"

Treatment:

Preventive therapy

- **Environmental control** (dust control, pets etc.)
- **Allergen immunotherapy** (vaccines etc.) *for modulating the immune response.

Pharmacological

- **Anti-Histamine** (H1-receptor antagonist)
- **Anti-Allergics**
  - -Cromolyn sodium (masts cell stabilizer)
  - -Montelukast (Leukotriene receptor antagonist)
- **Corticosteroids**
- **Decongestants** (alpha-adrenergic agonists)
- **Anti-Cholinergics**
- **Antibiotics** (if there's a bacterial infection)

What is Histamine?

Histamine is a chemical messenger mostly generated in mast cells that mediates a wide range of cellular responses including:

1. Allergic and inflammatory responses (H1 actions, We use H1 blockers in these conditions)
2. Gastric acid secretion (H2 actions, We use H2 blockers in these conditions)
3. Neurotransmission in parts of the brain (H3 action)
4. Regulating immune responses (H4)

Histamine has **no** clinical application but **Antihistamines** have important therapeutic applications.

Antihistamines (H1 receptor antagonists)

The term antihistamine without modifying objective refers to the **classic H1-receptor blockers**

- These drugs do not interfere with the formation or release of histamine
- They block the receptor mediated response of a target tissue

<table>
<tr><th>1st Gen</th><th>2nd Gen</th><th>3rd Gen</th></tr>
<tr><td>Alkylamine: Chlorpheniramine (Chlorphenamine)</td><td rowspan="3">Cetirizine</td><td rowspan="2">Levocetirizine</td></tr>
<tr><td>Ethanolamine: Dimenhydrinate
Diphenhydramine</td></tr>
<tr><td>Ethylenediamine: Antazoline</td><td rowspan="3">Fexofenadine
(least sedating)</td></tr>
<tr><td>Phenothiazine: Promethazine</td><td rowspan="4">Loratadine
(has advantage over other 2nd generation drugs that it has less effect on clarity “less sedating effect”)</td></tr>
<tr><td>Piperazine: Cyclizine</td></tr>
<tr><td>Piperidine: Azatidine</td><td rowspan="2">Desoloratadine</td></tr>
<tr><td>Ketotifen</td></tr>
<tr><td>Miscellaneous: Cyproheptadine</td><td></td><td></td></tr>
<tr><td>short duration

-Interactions with enzyme inhibitors (macrolides, antifungal, calcium antagonists)
-Additive pharmacodynamic ADRs</td><td colspan="2">long duration (better control)

-No drug interaction
-Minimal ADRs since they are more specific for H1 receptors</td></tr>
<tr><td>• The older 1st generation drugs are still widely used because they are effective and inexpensive.
• These drugs penetrate the BBB and cause sedation. Furthermore, they tend to interact with other receptors, producing a variety of unwanted adverse effects.</td><td colspan="2">• Second generation (non-sedating) agents are specific for H1 receptors and they carry polar groups, they do not penetrate the BBB causing less CNS depression</td></tr>
<tr><td colspan="3"><u>All are used systemically or topically</u></td></tr>
</table>

H1 Blockers Have:

Good control of:

- Rhinitis
- Conjunctivitis
- Urticaria
- Flu

Poor control of:

- Asthma
- Otitis
- Anaphylaxis
- Sinusitis
- Atopic dermatitis

Indications Linked to H1 Block

-Allergies
-Itching (Even if non allergic)
& very useful for insect bites.
-Others:
- Insomnia
- Sleep aid
- Vertigo
- Anxiety
- Cough

Antihistamines

Indications not linked to H1 block

Cholinergic	α Adrenergic	Serotonin	Histamine H1	~~Histamine H2~~
⬆Dry mouth ⬆Urinary retention ⬆Sinus tachycardia	⬆Hypotension ⬆Dizziness ⬆Reflex tachycardia	⬆Appetite (الشهية) 	⬇Allergic inflammation, itching, sneezing, rhinorrhea ⬇Neurotransmission in CNS ⬆Sedation ⬇Cognitive & psychomotor performance ⬆Appetite	

Side Effects Interactions

You have to differentiate very well between a-adrenergic and cholinergic. And know that it has therapeutic effects on rhinitis or any H1 receptors, while other blocking effects on muscarinic or adrenergic receptors are considered side effects.
So cardiac patients have to be careful when taking these drugs.

First line

1- Antihistamine Drugs

Actions ★

- The action of all the H1 receptor blocker is qualitatively similar
- They are much **more effective** in **preventing symptoms** than reversing them once they have occurred
- Most of these drugs have additional effects (especially 1st generation) unrelated to their blocking **H1 receptors**, which probably reflect binding of H1 antagonists to:
  - Cholinergic
  - Adrenergic
  - Serotonin receptors

Therapeutic Uses

1. Allergic rhinitis: relieves rhinorrhea, sneezing, and itching of eyes and nasal mucosa
2. Motion sickness , sleeping & anxiety.
3. Nausea and vomiting: promethazine
4.Common cold: dries out the nasal mucosa. Often combined with nasal decongestant and analgesics
5. Allergic dermatoses: can control itching associated with insect bites.

P.K

- H1 receptor blockers are well absorbed after oral administration
- Maximum serum levels occurring at 1-2 hours
- Average plasma half life is 4 to 6 hours
- have high bioavailability and distributed to all tissues including CNS
- Metabolized by the hepatic cytochrome P450 system
- Excretion occur via kidney except **fexofenadine** excreted in feces unchanged

ADRs

- **Sedation**
- **tinnitus**
- **fatigue**
- **dizziness**
- **blurred vision**
- **dry mouth.** these reactions were more evident in 1st generation.

mnemonics for antihistamine

Drug interaction

- **CNS depressants**
- **cholinesterase inhibitors**

Over-dose

The most **common** and **dangerous** effects of acute poisoning are those **on CNS**; **including hallucinations, excitement, ataxia** and **convulsions**

Ataxia: abnormal gait.

prevention

2- Anti-allergics

Type	Mast cell stabilizers	Leukotriene receptor antagonists
Example	Cromolyn (another name for cromoglycate) and Nedocromyl	Montelukast
M.O.A ★	⇩ Histamine release (mast cell stabilizers by inhibiting Cl channels), i.e. can act only as a prophylactic; **it does not antagonize released histamine**	Block leukotriene action note: we can't use antihistamine in asthma because the chemical mediator is leukotriene not histamine
Uses	**Used in children for prophylaxis of perennial allergic rhinitis** should be given on daily basis and **never stop abruptly** even if the child is showing an improvement	**for prophylaxis of lower respiratory tract allergies** (e.g. perennial allergen, exercise or aspirin induced asthma) **more than on upper respiratory tract allergies** (e.g. chronic rhinosinusitis)
ADRs	Can induce cough, wheezes, headache, rash, ...etc.	As in asthma

3- Corticosteroids

for severe cases of rhinitis and asthma

Example	**Beclomethasone**, **budesonide** and **fluticasone**
M.O.A ★	Anti-inflammatory → block phospholipase A2 → ⇩arachidonic acid synthesis → ⇩prostaglandins & leukotrienes Why corticosteroids are important in asthma? inhibits the synthesis of leukotrienes
Uses	Administered topically (inhaled) as steroid spray **Given if severe intermittent or moderate persistent symptoms** **Local corticosteroids are preferably used more than systemic ones. Why? To reduce the side effects.**
ADRs	Nasal irritation, fungal infection, hoarseness of voice

4- Decongestants

Type	Systemic	Topical
Example	Pseudoephedrine *has many side effects because of the ephedrine which is a sympathomimetic	**1-Phenylethylamines:** • Phenylephrine • Methoxamine **2-Imidazoline:** • Naphazoline • Oxymetazoline HCL • Xylometazoline HCL
M.O.A ★	**α-adrenergic agonists** *They make vasoconstriction of blood vessels in nasal mucosa & reduce the rhinorrhea.	
Uses	Treatment of nasal stuffiness	
ADRs	nervous , insomnia, tremors, palpitations, and hypertension.	Can cause Rebound nasal stuffiness (repeated administration 10 days -2 weeks)
C.I (Contraindication)	hypertension, heart failure, angina pectoris, hyperthyroidism. glaucoma.	----

5- Anticholinergics

Example	Ipratropium
M.O.A	----
Uses	-Nasal drops to control rhinorrhea (excess nasal secretions & discharge), so very effective in vasomotor rhinitis (watery hyper-secretion). -bronchodilator in asthma.
ADRs	Minimal systemic side effects (wheezing, bladder pain, cough producing mucus). **more is discussed in the Asthma & COPD lecture**

Which drug is the best for Vasomotor rhinitis ? **Ipratropium** ★

Found in male's lecture only

Effectiveness of different drug groups in controlling symptoms of Rhinitis

Drug Groups	Main Symptoms		
	Sneezing	Blockage Stuffiness	Secretions Rhinorrhea
Anti-Histamines	++	-	+
Anti-Allergics (Cromolyns)	+	+	+
Topical Corticosteroids	++	++	++
Decongestant	-	++	-
Anticholinergic	-	-	++

Treatment of cough

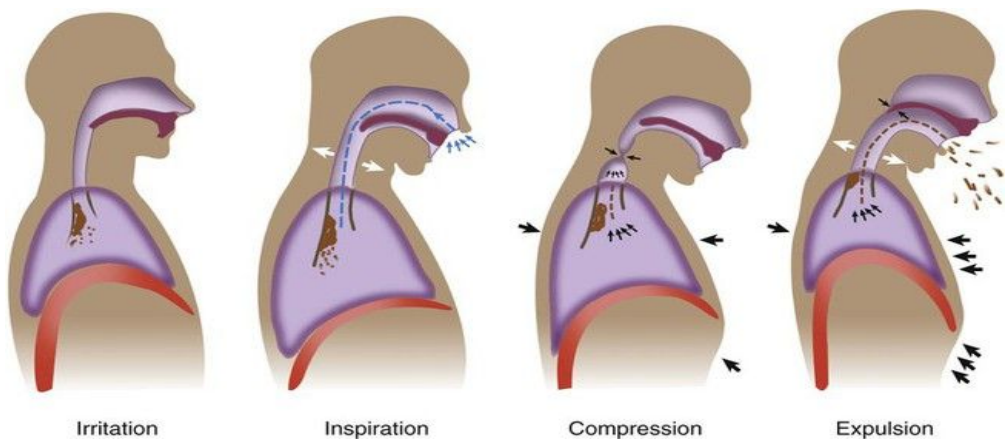
The respiratory tract is protected mainly by:

1- Mucociliary Clearance → ensures optimum tracheobronchial clearance by forming sputum (in optimum quantity & viscosity) exhaled by ciliary movements

2- Cough Reflex → exhales sputum out, if not optimally removed by the mucociliary clearance mechanism

What is Coughing?

- Coughing is sudden expulsion of air from the lungs through the epiglottis at an amazingly fast speed (~100 miles/ hr) to get rid of unwanted irritants.
- Abdominal & intercostal muscles contract, against the closed epiglottis → pressure ⬆ air is forcefully expelled to dislodge the triggering irritant.



Coughing

Types

- Productive or wet (Useful)

- Dry or irritant (Not useful) (secondary to irritant vapors, gases, infections, and cancer)

Treatment

For **Productive Cough**:

- Mucolytics مذيب للبلغم
- Expectorants طارد للبلغم

For **Non-productive (Dry) Cough**:

- Antitussive Agents
cough suppression

Expectorants :

Expectorants act by removal of mucous through different types of stimulations

Stimulation Type	Reflex Stimulation	Direct Stimulation
M.O.A	Irritate GIT ↓ stimulate gastropulmonary vagal reflex ↓ loosening and thinning of secretions	Stimulate secretory glands ↓ ⇧ respiratory fluids production
Example	**Guaifenesin**	**Iodinated glycerol,Na or K iodide/ acetate , Ammonium chloride, Ipecacuahna.**
ADRs	Dry mouth, chapped lips, risk of kidney stones **(increases uric acid excretion)**. *It is useful for patients with gout because it increases uric acid excretion.	Unpleasant metallic taste, hypersensitivity, hypothyroidism, swollen salivary glands (overstimulation of salivary secretion), & flare of old TB.
Uses	**Final outcome is that cough is indirectly diminished** 1.Common cold 2.Bronchitis 3.Pharyngitis 4.Chronic paranasal sinusitis	

Mucolytics:

Used to dissolve or breakdown mucus in the respiratory tract → mucus is less viscous → coughed up with more ease

Drug	Hypertonic Saline & NaHCO3	Steam inhalation	N-Acetyl Cysteine	Bromhexine & Ambroxol (Ambroxol is a metabolite of Bromhexine)	Pulmozyme Dornase Alpha or rhDNAase
M.O.A Mucolysis occurs by one or more of the following	⇩Viscoelasticity by ⇧water content	⇩Adhesiveness يقلل من ترابط جزيئات البلغم من خلال استنشاق البخار ويعتبر حل مؤقت	Breakdown S-S bonds in glycoprotein → less viscid mucous (Glycoproteins are found in mucous)	Synthesize serous mucus + activate ciliary clearance (عشان تطرد البلغم)	Cleavage of extracellular bacterial DNA, that contributes to viscosity of sputum in case of bacterial infection only
Overview			A free radical scavenger used in acetaminop-en overdose	⇧immune defence → ⇩antibiotics usage + ⇩pain in acute sore throat	A recombinant human -deoxyribo nuclease-1 enzyme genetically engineered that is neubilized + Full benefit appears within 3-7 days
ADRs			Bronchospasm , stomatitis, rhinorrhea, rash, nausea & vomiting	Rhinorrhea, lacrymation, gastric irritations, hypersensitivity	Voice changes, pharyngitis, laryngitis, rhinitis, chest pain, fever, rash
Uses	Most mucolytics are effective as adjuvant therapy in COPD, asthma, bronchitis (when there is excessive, thick mucus). In bronchiectasis, pneumonia & TB they are of partial benefit and hardly any benefit in cystic fibrosis & severe infections → give rhDNAase				

★ What's the M.O.A for **Bromhexine & Ambroxol** ? Synthesize serous mucus + activate ciliary clearance and increases the immune defence

Antitussive Drug

Stop or reduce cough by acting either:

- **Peripherally** — *acts on the receptors of the respiratory center.
- **Centrally** — *acts on the cough center itself.

1- Inhibitors of airway stretch receptors		
Location	**Use**	**Drug**
In Pharynx	Demulcents forms a protective coating (Soothing)	1- Lozenges 2- Gargles
In Larynx	Emollients forms a protective coating	1- Menthol 2- Eucalyptus
In Tracheobronchial Airway	Aerosols or inhalation of hot steam	1- Tincture benzoin compound 2-Eucalyptus
During bronchoscopy or bronchography	local anaesthetic aerosols	1- Lidocaine 2- Benzocaine 3- Tetracaine

2- Inhibitors of pulmonary stretch receptors in alveoli	
Drug	Benzonatate
M.O.A	⇩sensitivity (numbing) of receptors by local anesthetic action.
ADRs	Drowsiness, dizziness, dysphagia, allergic reactions. Overdose → mental confusion, hallucination, restlessness & tremors

Type	OPIOIDS	NON-OPIODS
Drugs	**1-Codeine** (very potent) **2-Pholcodine**	**1- Antihistamines (>sedating)** **2-Dextromethorphan**
M.O.A ★	activating μ opioid receptors	**Dextromethorphan increases threshold at cough center.** It has benefits over opioids in being: 1- As potent as codeine. 2- Less constipating. 3- No respiratory depression. 4- No inhibition of mucociliary clearance. 5- No addiction.
ADR for Dextromethorp		**Normal dose:** Nausea, vomiting, dizziness, rash & pruritus. **High dose:** Hallucinations + opiate like side effects on respiration & GIT.

QUIZ

MCQs:

1-A patient came to the ER with Rhinorrhea, Nasal stuffiness and sneezing. Which drug is the BEST to be given to him ?
A-Topical corticosteroid. B-Antihistamine.
C-Decongestants. D-Antiallergic.

2-One of the ADRs due to blockade of serotonin receptors is:
A-Increased BP. B-Increased dryness of mouth.
C-Increased Appetite. D-Increased sedation.

3-Which of these drugs belong to Non-Opioid Centrally acting antitussive?
A-Dextromethorphan. B-Codeine.
C-Menthol. D-Ledocaine.

4-A 43-years old woman came to the ER suffering from Acute Rhinitis , cough , itching and inability to sleep at night. Which of these drugs can you give to her safely ?
A-Eucalyptus. B-Ammonium Chloride.
C-Methoxamine. D-Fexofenadine.

5-One of these phrases is INCORRECT:
A-Decongestants act on alpha adrenergic receptors.
B-Ambroxol necessitates the use of antibiotics.
C-Guaifenesin May increase the risk of kidney stones.
D-the third generation of cyclizine is levocetirizine.

Answers
A, C, A, D, B

SAQ:

1-What are the possible ADRs caused by decongestants? list FOUR

2-How is the Antihistamine Drugs metabolized?

3-Ziyad, a 28 year-old airplane pilot suffers from allergic rhinitis, during his travels due to weather changes he developed a running nose, frequent sneezing, and nasal congestion. What are the best drugs to be prescribed to Ziyad in his condition? (mention at least two).

4-List FOUR indications of the Expectorants:

5-How can Corticosteroids treat Acute Rhinitis?

Answers:
1-nervous , insomnia, tremors, palpitation.
2-By Cytochrome P450 System.
3-Fexofenadine, Loratadine, Desoloratadine
4-Common cold,Bronchitis,Pharyngitis,Chronic paranasal sinusitis
5-Anti-inflammatory → block phospholipase A2 → arachidonic acid synthesis → prostaglandins & leukotrienes

pharmacology

Team 438

GOOD LUCK

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