Pharmacology of the Respiratory System

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Drugs for cough

- Pharyngeal Demulcents
  - Lozenges
  - Cough drops
  - Linctuses containing syrup

- Expectorants : increase secretion or reduce its viscosity.
  - Directly acting:
    - Sodium and potassium acetate or citrate : believed to increase secretion by salt action.
    - Potassium iodide:
      - Secreted by bronchial mucosa
      - Irritates the mucosa and increase the secretion.
      - Should not be given if bronchial mucosa is already inflamed
      - C/I in patients with iodine allergy
      - Less popular because of side effects

Mucolytics

- Bromhexine
  - Potent mucolytic and ,mucokinetic
  - Capable of inducing thin copious bronchial secretion
  - S/E : rhinorrhea and lacrimation
- Acetyl Cysteine:
  - Opens di-sulfide bonds in muco-proteins present in sputum and makes it less viscid
  - But, has to be administered directly into the respiratory tract.

Antitussives

- Codeine:
  - opium alkaloid
  - Qualitatively similar but less potent than morphine
  - More selective more cough center (naloxone blocks the action) and is used as standard antitussive
  - Acts for around 6 hrs
  - Abusive liability is low but present.
  - S/E: at higher doses: respiratory depression, drowsiness, unable to drive
  - Dose: 10-30 mg

Dextromethorphan

- Nonopioids
- Raises threshold of cough center.
- Doesnot depress mucociliary function of airway mucosa
- Practically devoid of mucociliary depressins action, constipation and addicting actions
- Activity not exerted thru opioid receptors (naloxone doesn't block the action)
- S/E: dizziness, nausea
- Dose: 10 – 20 mg

- DRUG: Albuterol
- CLASS: Sympathomimetic

- ***Actions***

1. **Agonist for Beta 2 adrenergic receptors; relaxing bronchial smooth muscle which results in bronchodilation**
2. **Minimal cardiac side effects**

- ***Indications:***

1. Treatment of bronchospasm associated with asthma, chronic bronchitis and emphysema
2. Prevention of exercise-induced bronchospasm

- ***Contraindications:***

1. **Hypersensitivity to sympathomimetics**
2. **Cardiac dysrhythmia**
3. **Tachycardia and tachydysrhythmias**

- ***Adverse Reactions:***

1. Excessive use may cause paradoxical bronchospasm and arrhythmias
2. Tachycardia, palpitations, angina, PVCs, hypotension, and hypertension
3. Tremors
4. Hyperglycemia
5. Peripheral vasodilation
6. Nervousness
7. Nausea/Vomiting

- ***Precautions:***

1. Diabetes
2. Hyperthyroidism
3. Cerebrovascular disease
4. Seizure disorders

- ***Dose:***

1. 2 inhalations with metered-dose inhaler, q 4-6 hours

- ***Incompatible/Reactions:***

1. Tricyclic antidepressants/monoamine oxidase inhibitors (MAOIs), may increase the effect of this drug
2. Other sympathomimetics
3. Beta blockers inhibit the effects

- ***Notes:***

Onset: 5-15 minutes
Peak: 30 minutes – 2 hours
Duration: 3-4 hours

1. Can be delivered by inhaler and nebulizer
2. Metabolized in the liver and excreted in the urine

Epinephrine

- CLASS: Sympathomimetic/Catecholamine

- ***Action:***

1. Direct effect on ***alpha*** and ***beta*** adrenergic receptor sites
2. Effects include:
   Alpha: bronchial, cutaneous, renal and visceral arteriolar constriction
   Beta 1: positive inotropic and chronotropic actions, increases automaticity
   Beta 2: bronchial smooth muscle relaxation and dilation of skeletal vasculature
3. Inhibits the release of histamine

- ***Indications:***

1. Cardiac arrest in general
2. Ventricular fibrillation
3. Asystole
4. Pulseless electrical activity
5. Infusion for profound hypotension associated with bradycardias, in combination with other pressors
6. Bronchospasm and bronchoconstriction of bronchial asthma and some forms of COPD
7. Anaphylaxis

- ***Contraindications:***

1. Uncorrected tachydysrhythmias
2. Underlying cardiovascular disease or hypertension
3. Glaucoma
4. Hypersensitivity to catecholamines
5. Hypothermia

Adverse Reactions

- Hypertension
- Ventricular arrhythmias
- Pulmonary edema
- Tachycardia
- Palpitations
- Anxiety
- Psychomotor agitation
- Nausea/Vomiting
- Pupil dilation
- Angina
- Nervousness
- Headache
- Dizziness
- Tremors
- Hallucinations
- Cerebral hemorrhage
- Anorexia

- ***Precautions:***

1. Due to the possibility of cardiovascular disease, epinephrine should be administered with caution in patients over 35 years of age (with respiratory problems or if they are conscious)
2. The patient should be carefully monitored for changes in pulse, blood pressure, and ECG after administration of epinephrine.
3. Because of its strong inotropic and chronotropic effects, epinephrine causes an increased myocardial O_2 demand
4. Hypovolemia (replenish volume first)
5. Diabetes mellitus
6. Hyperthyroidism
7. Prostatic hypertrophy
8. Must be protected from light
9. Tends to be deactivated by alkaline solutions (sodium bicarbonate)
10. Do not use with MAOIs or tricyclic antidepressants due to the danger of hypertensive crisis

- ***Dose:***

1. Cardiac dosage: 1:10,000
   a. 1 mg q 3-5 minutes (until the heart restarts)
   b. Intermediate: 2-5 mg q 3-5 minutes
   c. Escalating: 1 mg – 3 mg – 5 mg; 3 minutes apart
   d. High: 0.1 mg/kg q 3-5 minutes
2. Infusion: Mix 1 mg in 250 ml and run at 2-10 mcg/min
3. Anaphylaxis and Asthma: .1-.5 mg (1:1,000) SQ or IM

- ***Incompatible/Reactions:***

1. Potentiates other sympathomimetics
2. Patients on MAOIs, antihistamines, and tricyclic antidepressants may have heightened effects
3. Sodium bicarbonate – deactivates epinephrine
4. Nitrates
5. Lidocaine
6. Aminophylline
7. Don't mix the above drugs in the same syringe with epi; but can use in the same IV line – just flush between meds

- ***Notes:***

ONSET: Immediate

PEAK: Minutes

DURATION: Several minutes

Isoetharine

- CLASS: Sympathomimetic
- ***Actions:***

1. Beta 2 agonist (slight specificity); relaxes smooth muscle of bronchioles, vasculature, uterus

- ***Indications:***

1. Relieve bronchospasm associated with asthma, chronic bronchitis, and emphysema

- ***Contraindications:***

1. Hypersensitivity to sympathomimetics
2. Cardiac dysrhythmias
3. Tachycardia and tachydysrhythmias

- ***Adverse Reactions:***

1. Dose-related tachycardia, palpitations, tremors, nervousness, peripheral vasodilation, nausea/vomiting, transient hyperglycemia, life-threatening arrhythmias; multiple excessive doses can cause paradoxical bronchoconstriction
2. Angina
3. Hypertension
4. Headache, dizziness, anxiety, restlessness, hallucinations

- ***Precautions:***

1. Use with caution in patients with diabetes, hyperthyroidism, cardiovascular and cerebrovascular disease
2. Seizure disorders
3. Isoetharine contains acetone sodium bisulfite; a sulfite that may cause allergic-type reactions, including anaphylactic symptoms in certain susceptible individuals

- ***Dose:***

ADULT
1-2 inhalations with metered-dose inhaler
3-7 inhalations, via hand nebulizer q 4 hours

PEDIATRIC
Not recommended in children less than 12 years

- ***Incompatible/Reactions:***

1. Additive adverse effects with other beta agonists

- ***Notes:***

ONSET:	Immediate
PEAK:	5-15 minutes
DURATION:	1-4 hours

Metaproterenol

CLASS: Sympathomimetic

- ***Actions:***

1. Agonist for Beta 2 adrenergic receptors – acts directly on smooth muscle

- ***Indications:***

1. Relieve bronchospasm of COPD and Asthma

- ***Contraindications:***

1. Hypersensitivity to sympathomimetics
2. Hyperthyroidism
3. Cerebrovascular or cardiovascular disorders
4. Tachycardia and tachydysrhythmias

Adverse Reactions :

- Dose-related tachycardia
- Palpitations
- Nervousness
- Peripheral vasodilation
- Excessive use – lethal arrhythmias, paradoxical bronchospasm
- Hypertension
- Tremors, headache, dizziness, anxiety, hallucinations
- Nausea/vomiting

- ***Precautions:***

1. History of cardiovascular disease or hypertension
2. Seizures

- ***Dose:***

ADULT:
2-3 inhalations, q 3-4 hours
Metered-dose inhaler or nebulizer

PEDIATRICS:
Not recommended in children under 12 years

- ***Incompatible/Reactions:***

1. Beta blockers
2. MAOIs, tricyclic antidepressants
3. Potentiates other beta agonists

- ***Notes:***

ONSET: 1 minute

PEAK: 1 hour

DURATION: 1-5 hours with single dose
2-5 hours with repeated dose

Terbutaline Sulfate

CLASS: Sympathomimetic

- ***Actions:***

1. Beta 2 agonist – has an affinity for beta 2 receptors of bronchial, vascular, and uterine smooth muscle
2. At increased doses, beta 1 effects may occur

- ***Indications:***

1. Relieve bronchospasm associated with asthma, chronic bronchitis and emphysema (prevalent in patients over the age of 40 or with coronary artery disease)
2. Used in-hospital to stop pre-term labor

- ***Contraindications:***

1. Hypersensitivity to sympathomimetics
2. Cardiac dysrhythmias
3. Tachycardia and tachydysrhythmias
4. Glaucoma

- ***Adverse Reactions:***

1. Tachycardia, tremors, palpitations, nervousness and dizziness
2. Angina, PVCs, hypotension, and hypertension
3. Headache, anxiety, hallucinations
4. Nausea, vomiting
5. Bronchospasm

- ***Precautions:***

1. Used with caution to patients with a history of cardiovascular disease or hypertension
2. Seizure disorders
3. Thyroid disease
4. Diabetes

- ***Dose:***

ADULT:

0.25 mg SQ; repeat in 15-20 minutes

2 inhalations separated by a 60 second interval with a metered dose inhaler

4mg/7ml nebulizer mix

- ***Incompatible/Reactions:***

1. Alkaline solutions
2. Degrades when exposed to light for long periods of time

- ***Notes:***

ONSET: 15 minutes

PEAK: 30-60 minutes

DURATION: 90 minutes – 4 hours

Theophylline

- CLASS: Methylxanthine

- ***Actions:***

1. Beta 2 agonist; directly relaxes bronchial smooth muscle
2. Dilates pulmonary and coronary arterioles, decreasing pulmonary hypertension and increasing coronary blood flow
3. Slight positive chronotropic and inotropic effects
4. Strengthens diaphragmatic contractions by affecting intracellular calcium
5. Mild diuretic

- ***Actions:***

6. Stimulates CNS vomiting centers
7. Respiratory center stimulant
8. Stimulates vagal and vasomotor centers in the brain – can lead to decreased heart rate, vasoconstriction in the brain – depends on CNS or peripheral predominance

- ***Indications:***

1. Relieve bronchospasm associated with asthma, chronic bronchitis, emphysema, and pulmonary edema
2. Management of CHF and pulmonary edema

- ***Contraindications:***

1. Hypersensitivity to xanthene compounds (e.g. caffeine)
2. Cardiac dysrhythmias
3. Tachycardia and tachydysrhythmias

Adverse Reactions :

- Nausea/vomiting
- Hypotension
- Irritability
- Tachycardia
- Angina
- Flushing
- Diarrhea
- Increased respiratory rate
- Cardiac arrhythmias
- Tremors
- Seizures
- Palpitations
- Hypertension
- Anorexia

- ***Precautions:***

1. Caution if patient is already taking theophylline-containing medications
2. Caution to patients with a history of cardiovascular disease or hypertension
3. Thyroid disease
4. Active peptic ulcer
5. Hypotension may occur following rapid administration
6. May oppose the effects of beta blockers

- ***Dose:***

ADULT:
Loading dose of 6 mg/kg IV infusion over 20 minutes
Loading dose of 1 mg/kg IV infusion over 20 minutes if the patient has had theophylline products in the last 35 hours

- ***Incompatible/Reactions:***

1. Incompatible with most drugs
2. Simetidine, propranolol, erythromycin, and troleandomycin may increase the effects of the drug
3. Barbiturates, phenytoin, and smoking may decrease blood levels
4. May increase the effects of anticoagulants

- ***Notes:***

ONSET: 15 minutes:
PEAK: 30 minutes – 1 hour
DURATION: Averages 5 hours

Respiratory Pharmacology

- Respiratory meds are used for several purposes, the most obvious is the treatment of asthma.
- Class includes:

1. Cough suppressants
2. Nasal decongestants
3. Antihistamines

Anti-asthmatic Medications

- Asthma has two basic pathophysiologies:

1. Bronchoconstriction
2. Inflammation

- Treatment is aimed to relieve bronchospasm and decrease inflammation.
- Specific approaches are categorized as beta 2 selective sympathomimetics, nonselective sympathomimetics, methylxanthines, anticholinergics, glucocorticoids and leukotriene antagonists.

Beta 2 Specific Agents

- Albuterol (Proventil, Ventolin) is the prototype of this class.

1. These agents relax bronchial smooth muscle, resulting in bronchodilation and relief from bronchospasm.
2. These agents are first line therapy for acute shortness of breath.
3. Administered via metered dose inhaler or nebulizer.
4. Overall, these agents are very safe.

Nonselective Sympathomimetics

- Agents include: epinephrine, ephedrine, and isoproterenol
- Stimulate both beta 1 and beta 2 receptors, as well as alpha receptors.
- Rarely used to treat asthma because they have the undesired effects of increased peripheral vascular resistance and increased risks for tachycardias and other dysrhythmias.
- Epinephrine is the only nonselective sympathomimetic in common use today.

Methylxanthines

- CNS stimulants that have additional bronchodilatory properties.
- Used only when other drugs such as beta 2 specific agents are ineffective.
- Possibly block adenosine receptors.
- Prototype is theophylline, taken orally.
- Aminophylline, an IV medication, is rapidly metabolized into theophylline and, therefore, has identical effects.
- Chief side effects: nausea/vomiting, insomnia, restlessness, and dysrhythmias

Anticholinergics

- Ipratropium (Atrovent) is an atropine derivative given by nebulizer.
- Because stimulating the muscarinic receptors in the lungs results in constriction of bronchial smooth muscle, ipratropium, a muscarinic antagonist, causes bronchodilation.
- Ipratropium is inhaled, and has no systemic effects.
- Has an additive effect when used with beta 2 agonists.
- Most common side effect is dry mouth

Glucocorticoids

- Anti-inflammatory properties.
- Lower the production and release of inflammatory substances such as histamine, prostaglandins, and leukotrienes, and reduce mucus and edema secondary to decreasing vascular permeability.
- May be inhaled or taken orally, as well as IV.
- Prototype of inhaled glucocorticoid is beclomethasone.
- Prototype of oral glucocorticoid is prednisone.
- Administered as preventative care.

- When inhaled they cause few side effects.
- Side effects are due mostly to direct exposure on the oropharynx, and gargling after taking the drug can decrease the side effects.
- Side effects from the IV administrations of methylprednisolone in emergencies are not likely
- Long periods of administration can lead to adrenal suppression and hyperglycemia.

Cromolyn

- Another anti-inflammatory agent used is cromolyn (Intal), an inhaled powder.
- is the safest of all antiasthma agents.
- Only side effects are coughing or wheezing due to local irritation caused by the powder.
- Often used for preventing asthma in adults and children.

Leukotriene Antagonists

- Leukotrienes are mediators released from mast cells upon contact with allergens.
- Contribute powerfully to both inflammation and bronchoconstriction
- Can either block the synthesis of leukotrienes or block their receptors.
- Zileuton (Zyflo) is the prototype of those that block the synthesis of leukotrienes
- Zafirlukast (Accolate) is the prototype of those that block their receptors

DRUGS USED FOR RHINITIS AND COUGH

- Rhinitis: (inflammation of the nasal lining) comprises a group of symptoms including nasal congestion, itching, redness, sneezing, and rhinorrhea (runny nose).
- Allergic reactions or viral infections may cause it
- Drugs that treat the symptoms of rhinitis and cold are commonly found in over-the-counter remedies.
- Nasal decongestants, antihistamines, and cough suppressants are available in prescription medications.

Nasal Decongestants

- Nasal congestion is caused by dilated and engorged nasal capillaries.
- Drugs that constrict these capillaries are effective nasal decongestants.
- Main pharmacologic classification in this functional category is alpha 1 agonists
- Alpha 1 agonists may be given either topically or orally
- Examples of agents: phenylephrine, pseudoephedrine, and phenylpropanolamine, (administered in drops or mist)

Antihistamines

- Arrest the effects of histamine by blocking its receptors.
- ***Histamine*** is an endogenous substance that affects a wide variety of organs systems.
- Noted for its role in allergic reaction.
- Histamine binds with H1 receptors to cause vasodilation and increased capillary permeability (vasculature)
- In the lungs, H1 receptors cause bronchoconstriction
- In the gut, H2 receptors cause an increase in gastric acid release
- Histamine also acts as a neurotransmitter in the CNS.

Antihistamines

- Histamine is synthesized and stored in two types of granulocytes; tissue-bound mast cells and plasma-bound basophils
- Both types are full of secretory granules, which are vesicles containing inflammatory mediators such as histamine, leukotrienes, and prostaglandins, among others.
- When cells are exposed to allergens, they develop antibodies on their surfaces.
- On subsequent exposures, the antibodies bind with their specific allergen.

- Secretory granules then migrate towards the cell's exterior and fuse with the cell membrane. Causing them to release their contents.
- Histamines are useful in our immune systems.
- When our immune systems overreact do allergies such as hay fever or cedar fever send us running for the antihistamines
- Typical symptoms of allergic reaction include most of those associated with rhinitis.
- Severe allergic reactions (anaphylaxis) may cause hypotension

Antihistamines

- Antihistamines are at best only a secondary drug for treating anaphylaxis.
- Just as there are H1 and H2 histamine receptors, there are H1 and H2 histamine receptor antagonists.
- Most old antihistamines were H1 receptor antagonists, newer antihistamines are H2 receptor antagonists.
- Chief side effect is sedation (H1), newer generation do not cause this sedation effect (H2).
- First generation medications: alkylamines (chlorpheniramine [Chlor-Trimeton]), ethanolamines (diphenhydramine [Benadryl])

- Other first generation antihistamines: clemastine (Tavist), and phenothiazines (promethazine [Phenergan]).
- Some antihistamines also have significant anticholinergic properties: promethazine and dimenhydrinate (Dramamine), used for motion sickness.
- Second generation antihistamines include: terfenadine (Seldane), loratadine (Claritine), cetirizine (Zyrtec, and fexofenadine (Allegra).
- These agents do not cross the blood-brain barrier and therefore do not cause sedation.

Cough Suppressants

- Coughing is a complex reflex that depends on functions in the CNS, the PNS, and the respiratory muscles.
- It is a defense mechanism that aids the removal of foreign particles like smoke and dust.
- In general, treating a productive cough is not appropriate, as it is performing a useful function.
- An unproductive cough, usually results from an irritated oropharynx and can be troublesome.
- The three classifications of cough suppressants include one that is supported by evidence and two that are not.

- ***Antitussives***

1. Suppress the stimulus to cough in the CNS.
2. This functional class includes two specific pharmacologic types:
   a. Opioids
   b. Nonopioids
3. Two most common opioid antitussives are codeine and hydrocodone
4. Both inhibit the stimulus for coughing in the brain but also produce varying degrees of euphoria

5. The nonopioid antitussives do not have the potential for abuse.
   a. Dextromethoraphan
   b. Diphenhydramine
   c. Benzonatate (Tessalon)

- ***Expectorants:*** intended to increase the productivity of cough
- ***Mucolytics:*** make mucus more watery and easier to cough up
- Little data supports the effectiveness of either of these approaches to cough suppression