Pharmacology Team

Treatment of asthma

429 Medicine

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Definition of Asthma: Simply it is inflammation or hyper-reactivity of the airways .

hyper-reactivity: (over response to external stimulation)

Symptoms:

Coughing; shortness of Breath (dyspnea) and chest tightness and wheezing.

Causes

- Infection
- Emotional conditions
- Stress
- Exercise
- Pets
- Seasonal changes
- Some drugs as aspirin - Aspirin : Anti inflammatory drug not steroidal

Airways of the asthmatic patients are characterized by:

1. Inflammation
    - Swelling
    - Thick mucus production.
2. Bronchospasm
    - constriction of the muscles around the airways, causing the airways to become narrow.

Pahtophysiology of Asthma: (it is the key to understand Treatment).

1. Immunological model for immediate hypersensitivity (extrinsic asthma (Allergic Asthma)
2. Non-specific hyper-reactivity (Intrinsic asthma (non-Allergic))

It may be triggered by anxiety, stress, exercise, cold air, dry air, hyperventilation, smoke, viruses (chest infection) or other irritants (e.g: cleaning agents; food preservatives). In non-allergic asthma, the immune system is not involved in the reaction.

Airways Innervation

Efferent

1. Parasympathetic supply
    - M3 receptors in smooth muscles and glands.

    Bronchonstricton \ secretion gland increased so to treat asthma : antagonist of para
2. No sympathetic supply
    - B2 in smooth muscles and glands

    b2=bronchodilation + decrease secretion of glands so to treat we use Sympathomimetics

Afferents - from respiratory to CNS

1. Irritant receptors (vagal fibres): Upper airways

يصير لها stimulation مع الدخان مثلا

2. C-fiber receptors (sensory fibers) : Lower airways.

Classification of Drugs Used for Asthma:

1. **Bronchodilators**
a. b2-adrenergic agonists
b. Methylxanthines
c. Muscarinic-receptor antagonists
2. **Anti-inflammatory Drugs**
a. Cromolyn or nedocromil
b. Corticosteriods
c. Leukotrienes antagonists
d. Anti-immunoglobulin E (monoclonal antibody)

1. Bronchodilators

A. b2-adrenergic agonists

e.g.; Salbutamol; terbutaline (Short Acting, t1/2 4 hr)
Salmetrol; formetrol (Long Acting, t1/2 8 hr)

MOA (Mechanism of Action):

1- direct β2 stimulation ⟶ stimulate adenyl cyclase ⟶ Increase cAMP ⟶ bronchodilation
2- Inhibit mediators release from mast cells.
3- Increase mucus clearance by (increasing ciliary activity).

stimulation B2 = accumulation of adenylcyclase enzyme = cAMP increase = relaxation OF smooth muscle

PK (Pharmacokinetics):

Available as injections or oral but inhaled or nebulizer forms are more common.

b. Antimuscarinic Drugs:

History:

e.g.: Ipratropium (short acting); Tiotropium (long Acting)

PK: Only to be given by inhalation or by nebulizer ; with slow onset and longer duration as compared to salbutamol.

Pharmacodynamics

Bronchodilator
No anti-inflammatory action
Less effective than B2-agonists.
Minimal systemic side effects. (cause it is given inhalation).
Uses
-Chronic obstructive pulmonary diseases.
(these disease are mainly caused by parasymathatic stimulation = so the treatment is antagonsim of para)
-Adjuncts (helper) to B2 agonists & steroids for acute asthma
(if b2 no effect = combination with Muscarinicant antagonists = response increase)
-Patients intolerant to B2 agonists

c. Methyxanthins

e.g.: Theophyline; Aminophyline
MOA: 1. 1- are phosphodiestrase inhibitors
↑ cAMP → bronchodilation
2- Adenosine receptors antagonists (A1). A1 is responsible of bronchoconstriction .
Net result of 1, 2 is bronchodilation
3- Increase diaphragmatic contraction SO inspiration better
4- Stabilization of mast cell membrane
What is aminophyline? Theophyline +Ethylenediamine →It is a salt.
Pharmacological Effects :
1- relaxation of bronchial smooth muscles
2- CNS stimulation.
- stimulant effect on respiratory center.
- decrease fatigue & elevate mood.

if taken high dose from Theophylline :
- tremors رعشه, nervousness , insomnia أرق, convulsion

Skeletal muscles : ↑contraction of diaphragm → ventilation improvement
CVS:
+ ve Inotropic (↑ heart contractility)
tachycardia
+ ve chronotropic (↑ heart rate)
relaxation of smooth muscle in the blood vessels
vasodilatation ↓ blood pressure (hypotension)
GIT : Increase gastric acid secretions
relaxation of smooth muscle of GIT leads to increase motility
Kidney : weak diuretic action →(↑ renal blood flow)-→GFR ↑ =urine ↑ but these drugs aren't use as diuretic drug
PK: Absorbed orally (given after meals)
why?
because of gastric acid secretion =)
Metabolized in the liver by Cyt P450 enzymes (t ½ = 8 h)
Any drug has been modulate by cytocrom P450 -> has side effect drug drug interaction ->reflect on half life (T ½ could be increased or decreased depending on capacity of liver)

T ½ is decreased by (induce metabolism so the level of drug decrease)
Enzyme inducers (phenobarbitone-rifampicin)
T½ is increased by (inhibit metabolism so the level of drug increase)
Enzyme inhibitor (cimetidine, erythromycin) Cimetidine : used to treat peptic ulcer
NOTE : alcohol and smoking increase metabolism so decrease drug level

Uses
1. second line drug in asthma (theophylline is given orally as sustained-release preparation)
Any drug (SR)sustained-release ->has long duration of action=)
Why we increase duration -> to decrease frequency =)
2. For status asthmaticus "severe attack of bronchospasm" (aminophylline is given as slow infusion)

> Remember:
> First choice of bronchodilator is drugs short acting of β2 agonist
> =)

Side Effects: (= pharmacological action مرتبطة بالـ side effect دايم الـ)
low therapeutic index (ratio between LD50 and ED50)- [LD: lethal dose | ED: effective dose]
narrow safety margin
therapeutic index : LD50/ED50 indicates safety
less therapeutic index = less safety so the drug should be controlled
monitoring of theophylline blood level is necessary - " patient who takes this drug should check his / her blood level"

CNS side affect : seizure convulsionتشنج
CVS effects: hypotension, arrhythmia. / Nausea & vomiting

Bronchodilators

β2 - adrenoreceptor agonists

Non selective β agonists

Epinephrine

Comment

Potent

rapid action (maximum effect within 15 min).

S.C. or by inhalation by aerosol or nebulizer.

Duration of action 60-90 min

Drug of choice for acute anaphylaxis cause in anaphylaxis there are : bronchonctriction + hypotension

Disadvantages

1- Not effective orally.

2- Hyperglycemia # in Diabetes.

3- CVS side effects : Tachycardia, arrhythmia, hypertension # angina . not given to people who have : hypertension and CV disease

4- skeletal muscle tremor all the drug work on B2 receptor have this side effect

Isoprenaline

Potent bronchodilator

Given sc or via inhalation

(aerosol- nebulizer)

rapid action

(maximum effect

within 5 min)

Duration of action

60-90 min

Disadvantages

As epinephrine

Selective β2 –agonists

Short acting ß2 agonists

Salbutamol (albuterol) (inhalation Metered-dose inhaler, orally, I.V.)

Terbutaline (inhalation, S.C., orally)

Metaproterenol inhalation

have rapid onset of action (15-30 min), 5 min by inhalation

duration of action (3 – 4 hr)

used for symptomatic treatment of

bronchospasm (acute attack of asthma)

salbutamol is used for premature labor relaxition of uterus muscle.

NOTE : this type is the Best choice for acute attack of asthma

Long acting selective ß2 agonists

Salmeterol & formoterol:

Long acting bronchodilators (12 hours)

high lipid solubility (creates a depot effect)

Duration of action is to 12 hours due to high lipid solubility =

يمسكو بالريسبتور لمدة طويلة

salmeterol has slow onset of action

are not used to relieve acute episodes

used for nocturnal asthma (prophylaxis)

combined with corticosteroids excellent effect (synergism)

Bronchodilators : Muscarinic antagonists

Drugs	Kinetics	Pharmacodynamics	Uses
Ipratropium Tiotropium	Quaternary derivatives of atropine Not absorbed orally Given by aerosol inhalation Do not enter CNS delayed onset of action (30 min) Duration of action 3-5 hr	Bronchodilator No anti-inflammatory action Less effective than B2-agonists. Minimal systemic side effects cause it is given by inhalation .	1-Chronic obstructive pulmonary diseases 2-Adjuncts helper to B2 agonists & steroids for acute asthma 3-Patients intolerant to B2 agonists Tiotropium Longer duration (24 h) Used for COPD

Bronchodilators : Methylxanthines

Drugs	Mechanism of Action	Pharmacological Effects :	Pharmacokinetics	uses	Side Effects
Theophylline Aminophylline	1- are phosphodiestrase inhibitors ↑ cAMP → bronchodilation 2- Adenosine receptors antagonists (A1) 3- Increase diaphragmatic contraction 4- Stabilization of mast cell membrane	1- relaxation of bronchial smooth muscles 2- CNS stimulation. * stimulant effect on respiratory center. * decrease fatigue & elevate mood. * tremors, nervousness, insomnia, convulsion Skeletal muscles : ↑contraction of diaphragm → improve ventilation CVS: + ve Inotropic (↑ heart contractility) + ve chronotropic (↑ heart rate) vasodilatation ↓ blood pressure GIT : Increase gastric acid secretions, Kidney : weak diuretic action (↑ renal blood flow	Absorbed orally (given after meals) Metabolized in the liver by Cyt P450 enzymes (t ½ = 8 h) T ½ is decreased by Enzyme inducers (phenobarbitone-rifampicin) T½ is increased by Enzyme inhibitor (cimetidine, erythromycin)	-second line drug in asthma (theophylline is given orally as sustained-release preparation) -For status asthmaticus (aminophylline is given as slow infusion	low therapeutic index narrow safety margin monitoring of theophylline blood level is necessary CNS side effects: seizures CVS effects: hypotension, arrhythmia. Nausea & vomiting

Bronchodilators (relievers for bronchospasm)

Drugs		
B2 agonists **Salbutamol, terbutaline**	– Short acting – main choice in acute attack of asthma – Onhalation	Adenyl cyclase cAMP
Salmeterol, formoterol	Long acting, Prophylaxis Nocturnal asthma	
Antimuscarinics **Ipratropium (Short)** **Tiotropium (long)**	Main drugs For COPD Inhalation	Blocks M receptrors
Xanthine derivatives **Theophylline** **Aminophylline**	(orally) (parenterally)	• Inhibits phosphodiesterase↑ cAMP

Questions to remind u some points in lecture

When we use Epinephrine ?

anaphylactic reaction

Best choice to treat acute attack ?

B agonist short acting

Nocturnal asthma ?

B agonist long acting

Drug use in Chronic obstructive pulmonary diseases?

Muscarinicant antagonists

When we use Epinephrine ??

anaphylactic reaction

Best choice to treat acute attack ?

B2 agonist short acting

Nocturnal asthma ?

B2 agonist long acting

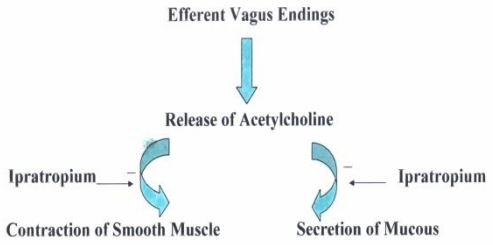
Drug use in Chronic obstructive pulmonary diseases As main drug?

Muscarinic antagonists

Aminophylline is one of the Xanthine derivatives Used for?

status asthmaticus Iv infusion

Done by : Badra'a

Summarized review			
1.Bronchodilators			
Drugs Used for Asthma	a. b2 adrenergic agonists	b.Methylxanthines **Theophyline** & **Aminophyline**	c. Muscarinic-receptor antagonists
Drug	**Salbutamol** & **terbutaline** (Short Acting, t1/2 4 hr) **Salmetrol** & **formetrol** (Long Acting, t1/2 8 hr)	**Theophyline** & **Aminophyline**	**Ipratropium** (short acting)it's atropine + CH3 (quatraly) & **Tiotropium** (long Acting)
Mechanism of action	Stim. b2-adrenoceptors leading to smooth muscle relaxation via c-AMP (see Figure 20-1). Also, may prevent activation of mast cells	1. Bronchodilation via increasing the level of c-AMP by inhibition of phosphodieasterase. 2. Theophyline is an universal antagonist at adenosine receptors ??, thus causing Bronchial smooth muscle relaxation	 CONCLUSION: Ipratropium is useful as a bronchodilator and also decreases mucus production (Suitable for COPD). (Alhaider, 1421 H).
Pharmacokinetics	Available as injections or oral but inhaled or nebulizer forms are more common WHY? Because it may cause more side effect when given I.V. or Orally	Available in oral (e.g.: Sustained release) or injectable forms. What is aminophyline? Theophyline + Ethylenediamine It is a salt.	**PK:** Only to be given by inhalation or by nebulizer, with slow onset and longer duration as compared to salbutamol.
COPD patient	**It cannot be given to copd patient**	**Why do theophyline not commonly used?** It used to be given with B2 to be long acting but they invented a long acting drug * wide side affects	Good for COPD cause decrease in the secretion of mucus cause bronchodilation