Drug therapy for bronchial asthma

Bronchodilators

1- β2 agonists

A. Non-selective β-agonists (β1, β_2): Adrenaline (used only in bronchial asthma due to anaphylactic shock)
Selective β_2 agonists:
- Short-acting: salbutomal, terbutaline (4-6 H)
- Long acting: salmeterol and formeterol (12 H)

1) Salbutamol: Short acting beta2 agonist (SABA)
- Selective stimulant of β_2 adrenergic receptors
- Selective action on the bronchi
- Given orally & by inhalation

2) Terbutaline: Short acting beta2 agonist (SABA)
- Like salbutamol but has a delayed onset of action

3) Salmeterol & Formoterol: long acting beta2 agonist (LABA)
- Selective long-acting β_2 agonists
- Given by inhalation for long-term prevention of bronchial asthma
- Should be combined with inhaled corticosteroids to avoid tolerance

Adverse effects:
- Tremors
- Tachycardia: Arrhythmia may occur in patients with underlying cardiac diseases eg, ischemic heart disease
- Tolerance
- Hypokalemia

Note: Adverse effects occur more frequently with oral preparations than with inhalation
Note: Nebulizers provide more quantity of the drug than MDIs, so nebulized β2 agonists can cause more adverse effect

2- Methylxanthines (Aminophylline & Theophylline)

Mechanism of action:
- PDE inhibitors → ? cAMP which causes redistribution of intracellular Ca^{+2}→ bronchodilatation
- Block adenosine receptors → bronchodilatation
- Improve diaphragmatic contraction & ventilatory response to hypoxia
- ? mediators release from mast cell

Pharmacokinetics:
- Theophylline is absorbed by all routes
- Distributed all over the body & passes BBB and placental barrier
- Metabolized in liver (by xanthine oxidase) into soluble methyluric acid (not precipitated in the joints → not contraindicated in gout)
- Narrow therapeutic window with low safety

Pharmacological actions:
- Relaxation of the smooth muscle (bronchial, intestinal, biliary, ureteric and vascular smooth muscles "except cerebral blood vessels" → vasodilatation and hypotension)
- CVS: Direct: positive inotropic & chronotropic effects - VD (hypotension)
Central: stimulation of CIC (bradycardia) & VMC (hypertension)
- Large & rapid IV injection → hypotension & arrhythmia.

Precautions:
- Monitoring of plasma level (to avoid toxicity)
- Slow IV administration to avoid hypotension & arrhythmia

Note: Roflumilast
- A selective PDE-4 inhibitor → has selective action on airways & inflammatory cells → fewer adverse effects than methylxanthines
- Approved for treatment of COPD (chronic obstructive disease)

3- Muscarinic (M) Antagonists

- Atropine (tertiary amine) blocks bronchial M receptors, but it is not effective in bronchial asthma because:
1. Cholinergic pathways play a minor role in the pathogenesis of bronchial asthma
2. Non-selective effects:
- Dryness of bronchial secretions
- ? Muco-ciliary function15

- Ipratropium bromide:
✓ Quaternary ammonium derivative of atropine
✓ Minimal amounts are absorbed → no systemic adverse effects
✓ More selective (causes bronchodilation without effects on sputum viscosity or ciliary function)
✓ No central effects
✓ Given by inhalation & can be combined with β_2 agonists
✓ Short-acting → used 3-4 times daily

- Tiotropium differs from ipratropium in the following
✓ Long-acting (given once/day)
✓ Given by inhalation
✓ Approved for treatment of COPD with no cardiac adverse effects

Anti-inflammatory drugs

1- Corticosteroids

Mechanism of action:
✓ ? Synthesis of lipocortin → ? PLA_2 activity → ? arachidonic acid, PGs and LTs synthesis
✓ Immunosuppressive action (? antibody synthesis) & inhibition of Ag/Ab reaction & mast cell stabilization
✓ ? Capillary permeability & reduce mucosal edema
✓ ? Catecholamines effect through:
- Block neuronal reuptake
- ? Methylation of noradrenaline to adrenaline

Uses in bronchial asthma:
✓ Prophylaxis (in between attacks)
✓ Repeated nocturnal asthma
✓ Acute severe asthma
Preparations:
A. Inhalation: beclomethasone, budesonide, fluticasone (long-acting)
B. Parenteral: methylprednisolone, hydrocortisone, dexamethasone, ACTH
C. Oral: prednisolone

Adverse effects:
A. Inhalation:
✓ Oral moniliasis (treated by nystatin)
✓ Dysphonia due to weakness (myopathy) of adductor muscle of the cord
B. Suppressive effects: adrenocortical suppression
C. Cushing's syndrome (with the use of large doses of corticosteroids)
D. Metabolic: hypokalemia, hyperglycemia, salt & water retention, weight gain and hypertension
E. Cataract

3- Mast cell stabilizers

Members:
1. Disodium cromoglycate (Cromolyn sodium)
2. Ketotifen
✓ They are not bronchodilators
✓ So, they cannot relieve acute attacks of asthma
✓ They can be effective only if given before the exposure the antigen
✓ Mechanism: stabilization of mast cell membrane (possibly by blocking calcium influx) → ? release of allergic mediators eg, histamine & LTs

✓ They are useful chiefly for asthma prophylaxis, particularly children & young adults
✓ Ketotifen has additional antihistamine effect
✓ Route:
- Disodium cromoglycate: inhalation
❖ It is also available as nasal spray for allergic rhinitis & as eye drops for allergic conjunctivitis
- Ketotifen: oral administration
✓ Adverse effects:
- Disodium cromoglycate:
❖ Local irritation: bronchospasm & cough
- Ketotifen:
❖ Drowsiness

Supportive treatment

2- Leukotriene Antagonists

- They include:
1. LT receptor antagonists (Montelukast & zafirlukast)
2. 5-LOX inhibitors (zileuton): ? LTs synthesis
- Pharmacokinetics:
✓ All members are given orally
✓ Zafirlukast absorption is affected by food
✓ They are metabolized by liver

- Uses:
✓ prophylaxis of bronchial asthma especially aspirin-induced asthma
- Adverse effects:
✓ Liver toxicity:
❖ Regular monitoring of liver transaminases is required if their levels exceeded 3-5 times the normal level, these drugs should be discontinued
❖ More reported with zileuton
✓ Systemic vasculitis (Churg-Strauss syndrome): rare

4-Omalizumab

✓ Selectively binds to human IGE → inhibits IGE binding to its receptor on mast cells & basophils surface → ? release of inflammatory mediators
✓ It decreases severity and frequency of asthma exacerbations
✓ Used in patients resistant to conventional therapy (β2 agonists & inhaled corticosteroids)
✓ Its use is limited by its high cost