Pharmacology - RS

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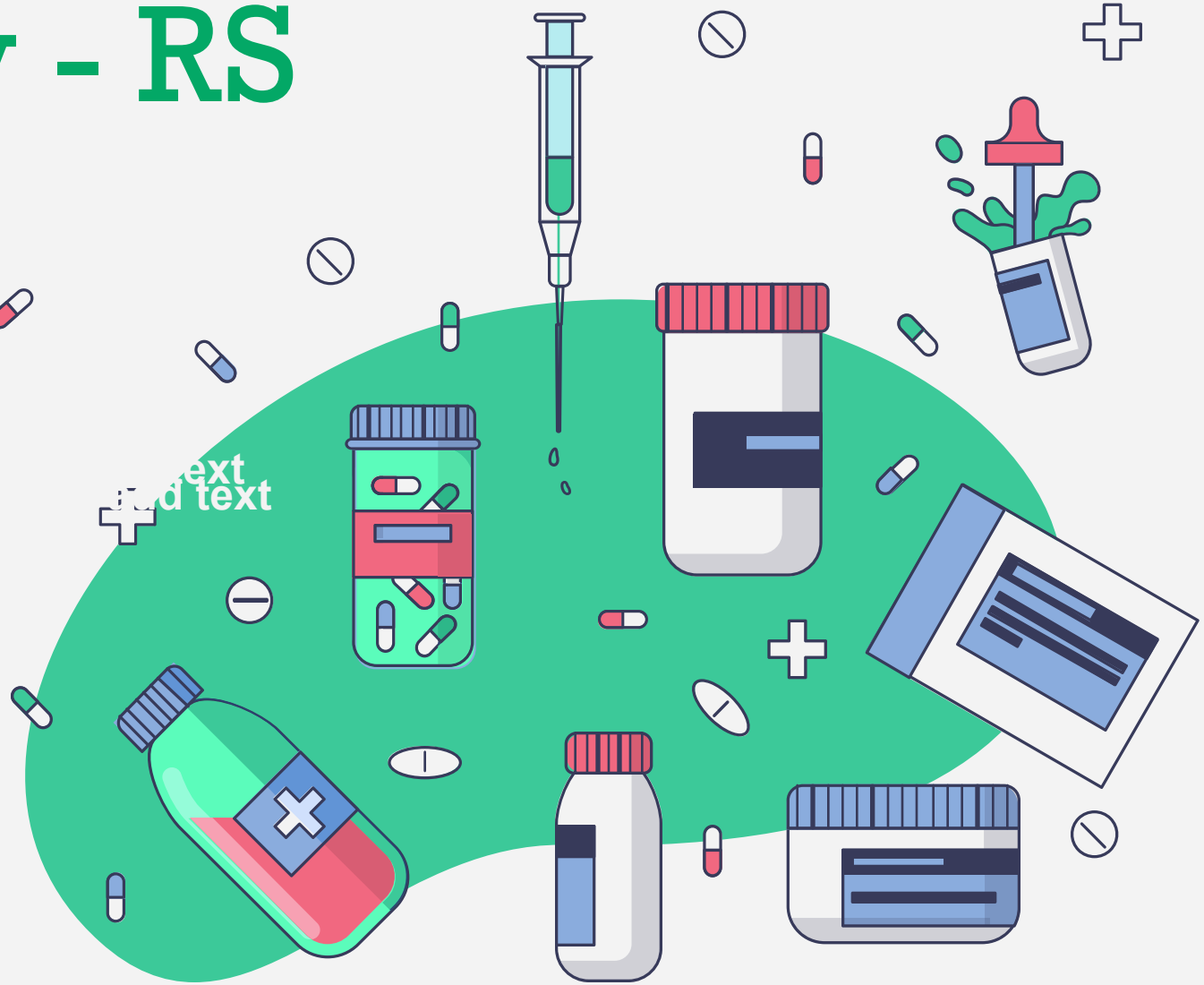

النادي الطلابي
كلية الطب

Treatment of Bronchial Asthma

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Methylxanthines

- **Theophylline.**
- **Aminophylline.**

Methylxanthines came before beta 2 agonists
They are tea,coffee,cacao

Were the mainstay treatment(60s-70s).withdrawn then came back .

Because they have low therapeutic index >> should be monitored

Oral ,rectal and Intravenous.

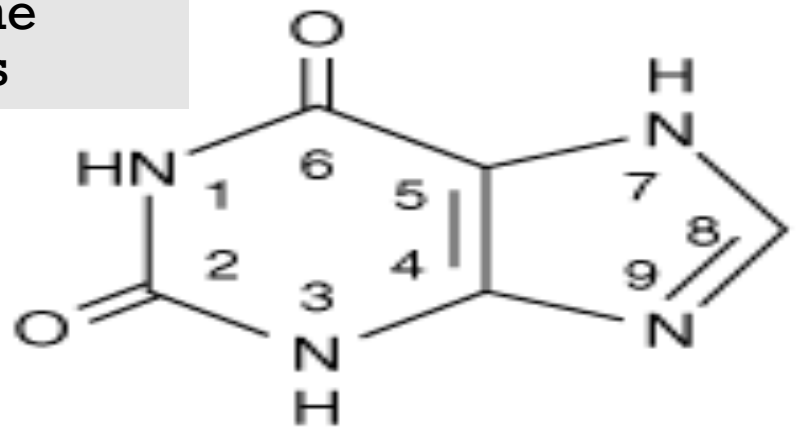
CNS stimulants

Cardiovascular stimulants; arrhythmias.

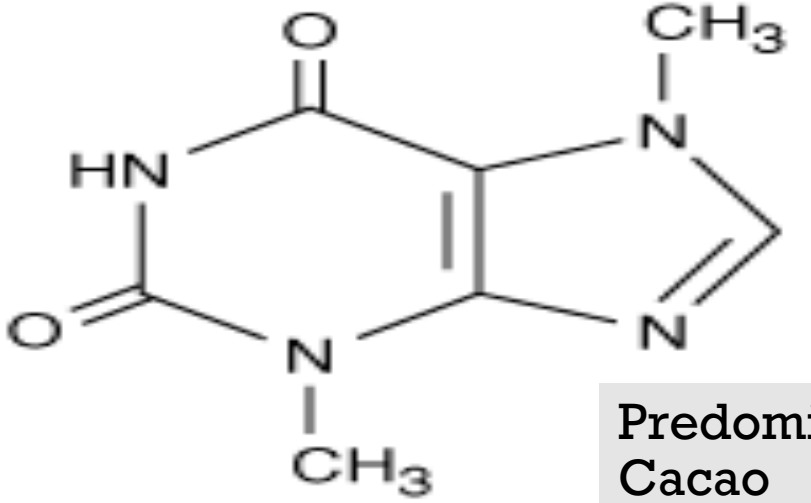
Nausea, GIT irritation, diarrhea.

METHYLXANTHINE DRUGS

Xanthine nucleus

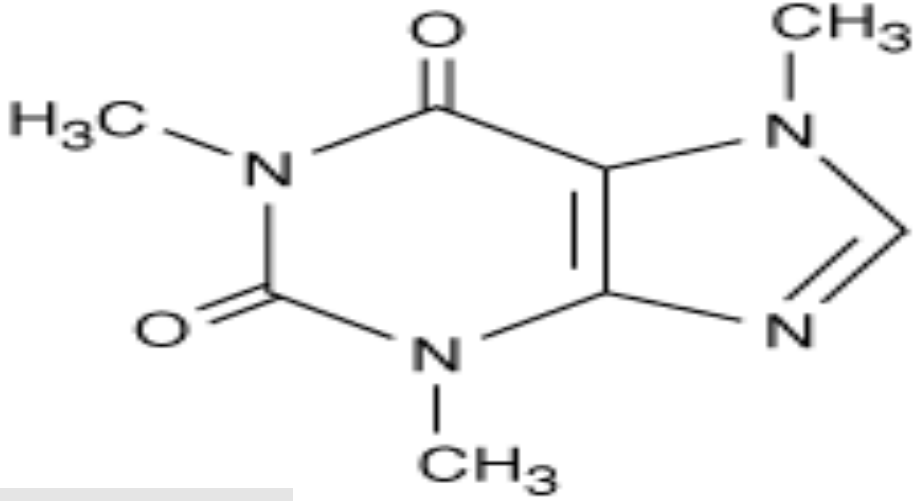


Xanthine



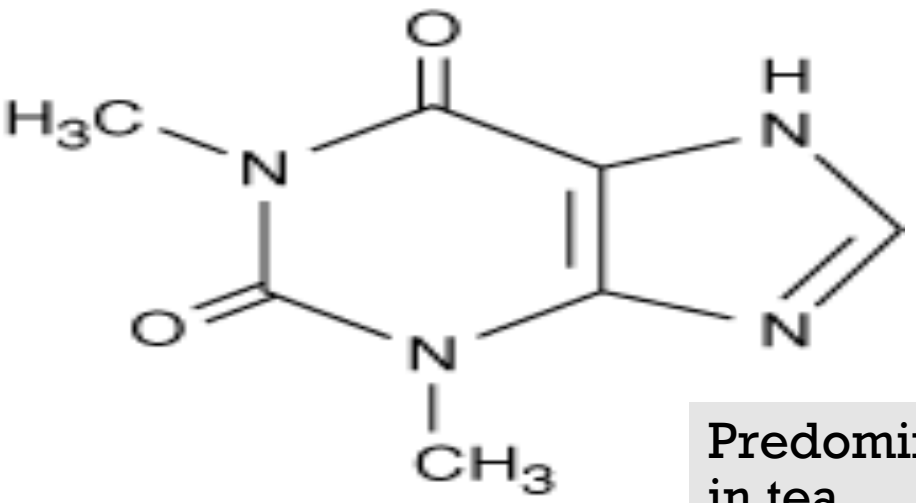
Theobromine

Predominately in Cacao



Caffeine

Predominately in Coffee



Theophylline

Predominately in tea

Mechanism of Action of Methylxanthines

- **Phosphodiesterase inhibition.**

Phosphodiesterase breaks down cAMP which is important for smooth muscle relaxation

- **Adenosine receptor antagonism (adenosine causes bronchoconstriction) .**
- **Antiinflammatory activity.**

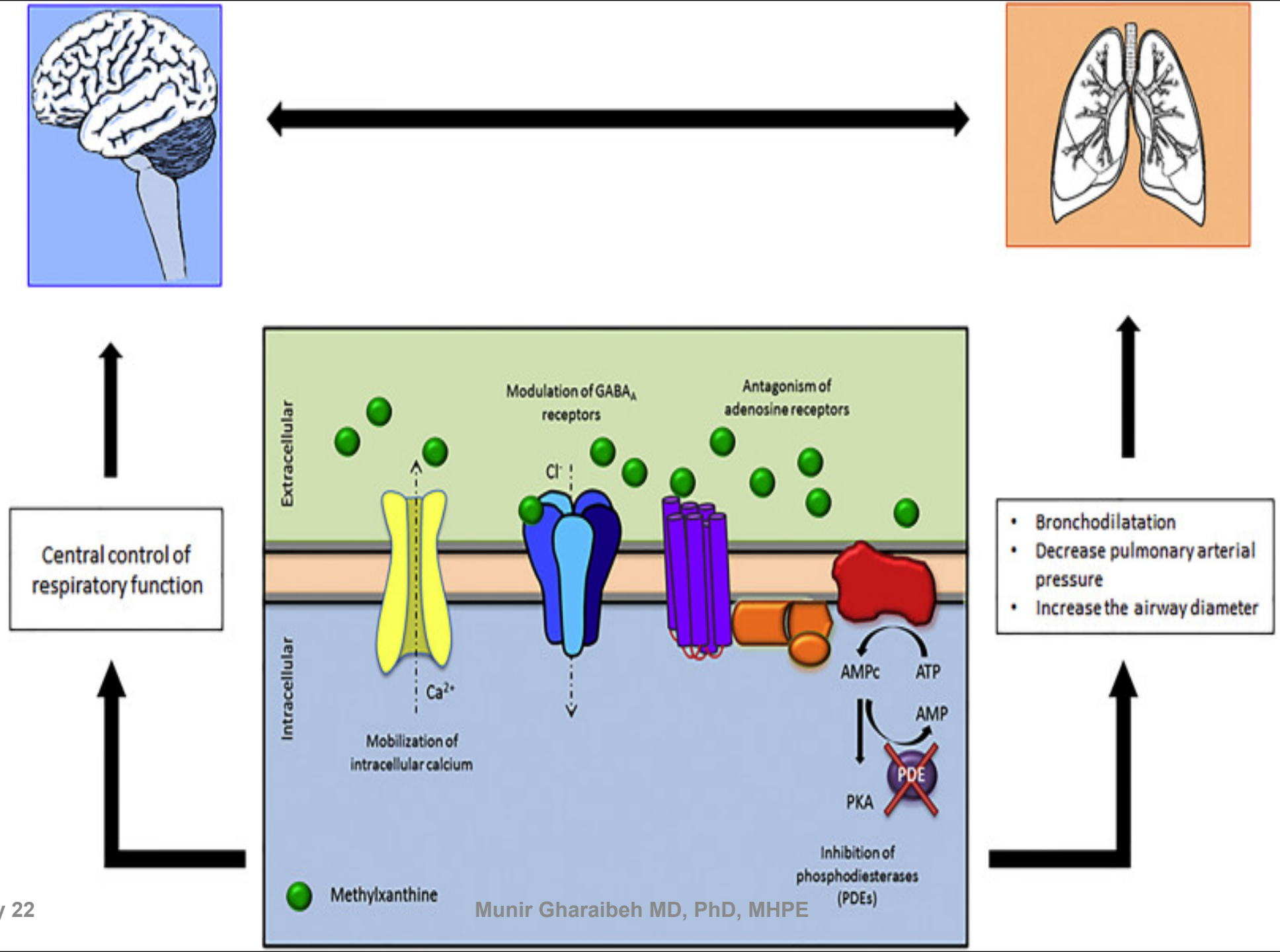
Good for bronchial asthma which is characterized by bronchoconstriction + inflammation

Methylxanthines

- Theophylline and its derivatives are most commonly used for the treatment of COPD and asthma.
- Caffeine, theophylline and theobromine are naturally occurring xanthine alkaloids which have qualitatively similar actions.

- ***Mechanism of action:***

  - Methylxanthines inhibits cyclic nucleotide phosphodiesterase (PDEs), thereby preventing conversion of cAMP and cGMP to 5'-AMP and 5'-GMP, respectively. Inhibition of PDEs will lead to an accumulation of intracellular cAMP and cGMP. Bronchodilataion, cardiac stimulation and vasodilatation occur when cAMP level rises in the concerned cells. Theophylline and related methylxanthines are relatively nonselective in the **PDE subtypes inhibitor**.
  - Theophylline is a competitive **antagonist at adenosine receptors**. Adenosine can cause bronchoconstriction in asthmatics and potentiate immunologically induced mediator release from human lung mast cells. Methylxanthines inhibits the adenosine action thereby casing bronchodilataion.


Central control of respiratory function
Extracellular
Intracellular
Modulation of GABA$_A$ receptors
Antagonism of adenosine receptors
Cl^-
Ca^{2+}
Mobilization of intracellular calcium
AMPc
ATP
AMP
PDE
PKA
Inhibition of phosphodiesterases (PDEs)
Methylxanthine
• Bronchodilatation
• Decrease pulmonary arterial pressure
• Increase the airway diameter

Problems with Methylxanthines

Therapeutic index is low

Optimal dosing is very difficult.

Wide inter-individual variation in the rate of hepatic metabolism.

Genetic variation & life style

Half life: 3-16 hours.

Food and drug interactions (erythromycins and ciprofloxacin).

Blood assay is a routine.

Used in the treatment of respiratory tract infections and we know that asthma patients could have bacterial infections so drug drug interactions could happen

Theophylline Returns

- **Resurgence of an old friend:**

Use of low dose theophylline, with mean plasma level of 36 µmol/ml (7 µg/ml), significantly inhibits the Late Asthmatic Reaction (LAR) and airway inflammatory infiltration.

So theophyllines are very effective if we could avoid the side effects and we cannot except by blood monitoring

Anticholinergic Agents

- **Atropine:**

And can be given by injection

Can be inhaled, but; can cause systemic side effects.

Redness, tachycardia

Impairs mucociliary clearance leading to dryness, and consequently, impaired clearance of airway secretions.

Although it causes bronchodilation

Parasympathetic > > bronchoconstriction
Sympathetic >> bronchodilation

Acetylcholine >>bronchoconstriction + bradycardia + syncope >> but short action

Anticholinergic Agents

- **Ipratropium Bromide Inhaler:**

Poorly absorbed from respiratory mucosa.

Does not impair clearance of airway secretions.

Causes minimal cardiac or central effects.

Anticholinergic Agents

- **Ipratropium Bromide Inhaler:**
- **Metered dose inhaler and as a solution for nebulization.** Locally not IV or oral
- **Mainly for COPD, not for asthma, because of slow onset (10-15 minutes) and low potency.**
- **Might be very useful in special conditions :**
  (beta blocker- induced asthma, resistant attacks, cardiac patients)

Beta blockers cause bronchoconstriction >> should be antagonized by beta agonists >> but beta agonists (E + NE) cause cardiac stimulation which will worsen the patient condition >> se we use other drugs which don't work on beta receptors >> ipratropium bromide

Anti-inflammatory Agents and Alternative Therapy

- **Coricosteroids.**
- **Inhibitors of Mast Cell Degranulation.**
- **Leukotriene Pathway Modifiers.**
- **Immunomodulatory Agents.**

Corticosteroids(1950s)

الدوا السحري

- Inhibit the synthesis and release of many chemical mediators (histamine, PGs and cytokines).
- Suppress the inflammatory cell influx and process.
- Relax bronchial smooth muscle.
- Enhance beta-adrenergic responsiveness (upregulate β receptors).
- Increase synthesis of adrenergic mediators.
- Decrease quantity and viscosity of secretions.
- Inhibit IgE synthesis.
- Decrease microvascular permeability.

Corticosteroids

Highly lipophilic, enter the cytosole.

- **Bind to cytosolic receptors.**
- **The drug-receptor complex enters the nucleus.**
- **Decrease transcription of genes coding for pro inflammatory cytokines.**
- **Take several hours to days to work.**

Corticosteroids

Short term systemic use in severe refractory attacks.

Long term use for ”Steroid Dependant” asthma.

We start with high doses then decrease the dose then stop it

Start with high dose then
Continue on a small dose

Corticosteroids

- **Systemic Use:**

  Oral or injectable

  (Cortisone, Prednisolone, Dexamethasone)

- **Inhalation:**

Aerosol treatment is the most effective way to avoid the systemic adverse effects

(Beclomethasone, Triamcinolone, Flunisolide, Budesonide, Fluticasone).

Corticosteroids

- **Local Side Effects:**

Hoarseness of voice (dysphonia), sore throat and cough.

Candida infection.

Some people are sensitive or allergic to inhalers >> give beta 2 agonists before corticosteroids

- **Systemic Side Effects:**

High doses, long period

Osteoporosis, cataract, glaucoma, growth retardation, adrenal suppression, CNS effects and behavioral disturbances, increased susceptibility to infections, and teratogenicity.

Because Sudden withdrawal as the ACTH is suppressed

Not recommended in pregnancy

Inhibitors of Mast Cell Degranulation

Mast cell releases histamine (bronchoconstrictor) when it breaks down

- **Cromolyn Na and Nedocromil Na:**

Inhibit the release of inflammatory mediators from mast cells (*Mast Cell Stabilizers*).

Prophylactic for mild to moderate asthma.

Regular use (4 times daily).

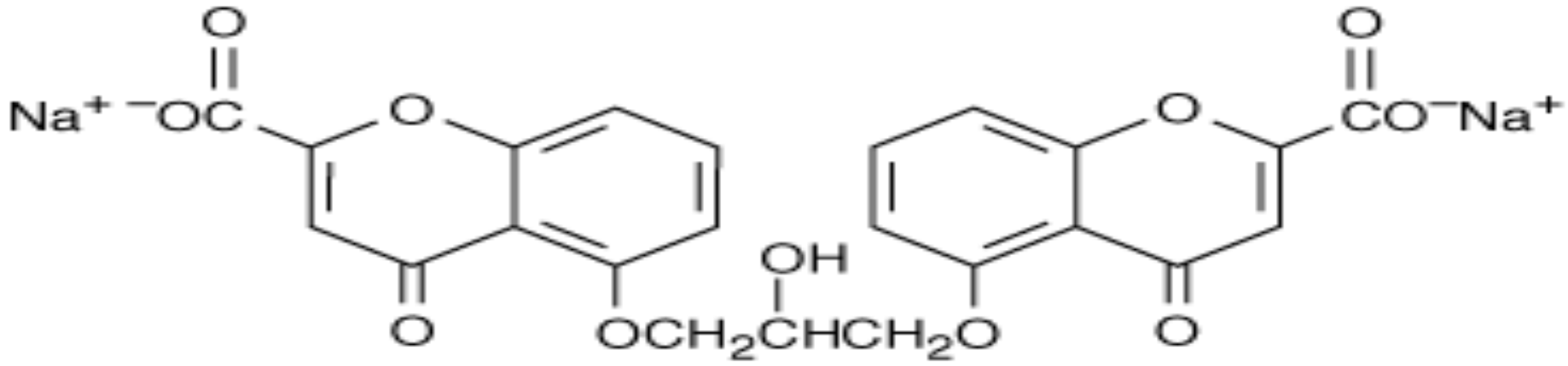
Not for acute asthma.

Phosphorylates a cell membrane protein, so, mediator release is inhibited despite antigen-IgE interaction.

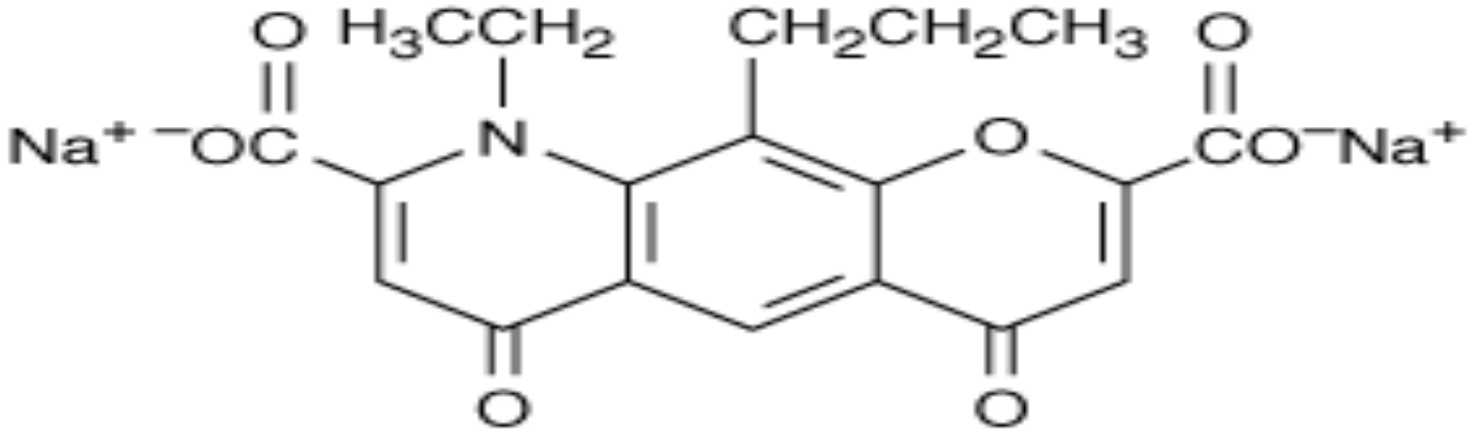
Might decrease Ca++.

Might decrease neural pathways, plasma exudation and inflammation in general.

Complete absence of side effects.



Cromolyn sodium



Nedocromil sodium

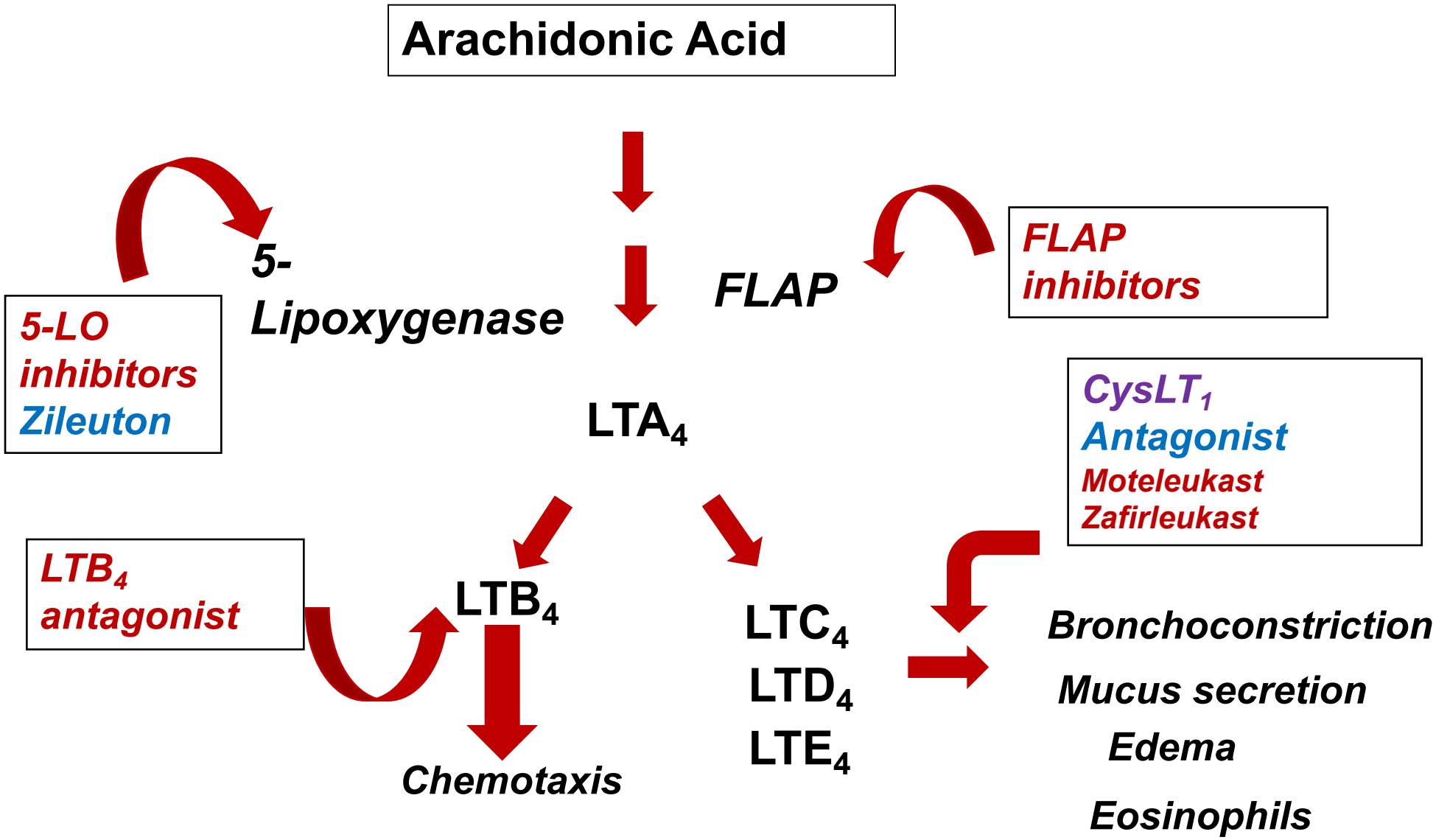
Dr skipped this

Leukotrienes

- **Synthesized by mast cells and eosinophils.**
- **They are 1000-fold more potent than histamine in stimulating airway smooth muscle constriction.**
- **They also promote microvascular leakage, mucus secretion and eosinophil chemotaxis.**
- **Pathway augmented by COX inhibitors (i.e. NSAIDs)**

When COX is inhibited >> shunt to leukotrienes

Leukotriene Modification



Leukotriene Pathway Modifiers

- **3-5% of adults with asthma, have “aspirin sensitivity’.**
- **This reaction is not an allergic response, can be induced by many different chemicals (tetrazine, FDC Color #5), and does not involve IgE antibody response.**

الصبغة الصفرة (ميرندا ، كنافة ، عصير برتقال أبو الشلن)

- **Patients produce high levels of cysteinyl leukotrienes in response to COX inhibitors, probably by shunting of arachidonic acid into leukotriene pathway.**
- **Abnormality of the promotor region of the gene for LTC4 synthase, leading to overexpression of the enzyme leading to increased conversion of LTA4 to LTC4.**

Leukotriene Pathway Modifiers

- **Inhibitors of 5-Lipoxygenase enzyme:**

Zileuton: for acute and chronic treatment, 4 times daily, hepatotoxic.

- **Antagonists of Cysteinyl Leukotriene Receptors:**

Montelukast.

Zafirlukast.

Some patients improve, others do not (Churg-Strauss Syndrome.

Leukotriene Pathway Modifiers

- **Churg-Strauss Syndrome:**

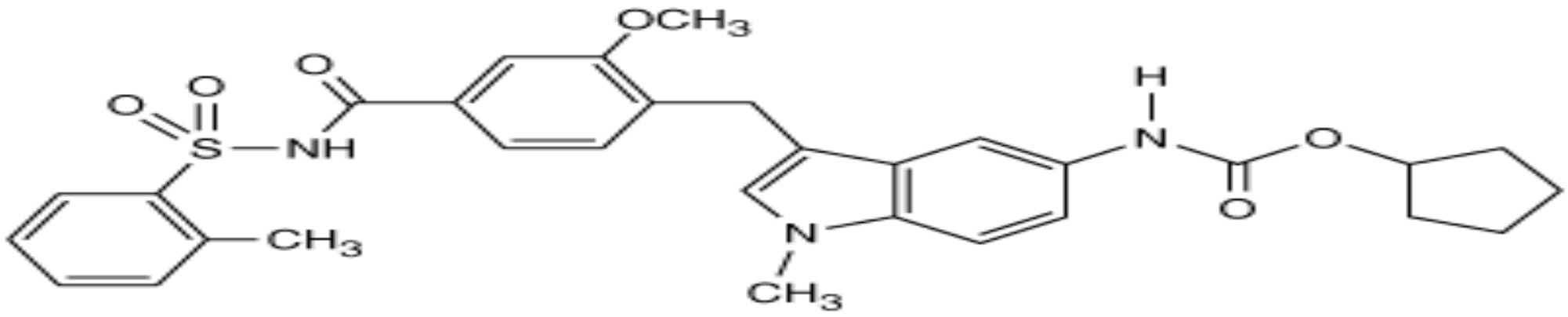
Rare reaction in newly treated asthmatic patients.

Severe inflammatory reaction, pulmonary infiltration, neuropathy, skin rash, and cardiomyopathy.

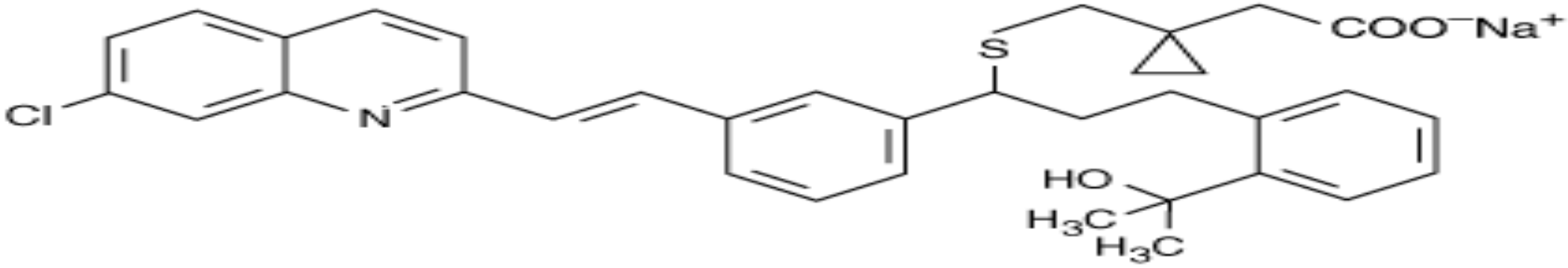
A common finding is systemic vasculitis with eosinophilic infiltration and granuloma formation.

Could also be due to unmasking of vasculitis after steroid withdrawal.

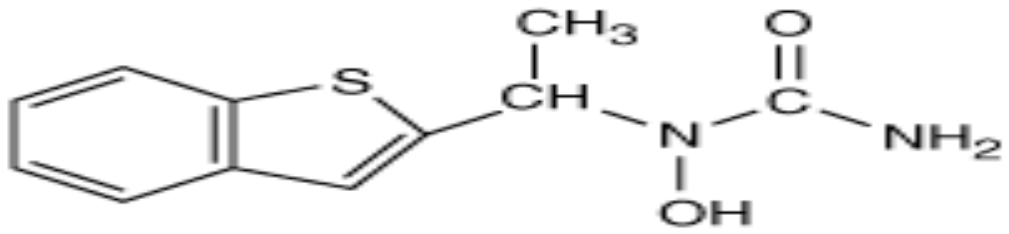
Leukotriene Pathway Inhibitors



Zafirlukast



Montelukast



Zileuton

Dr skipped this

Montelukast / Beta agonist study

Combination

- ↓ percent of patients needing systemic use of corticosteroids by 39%

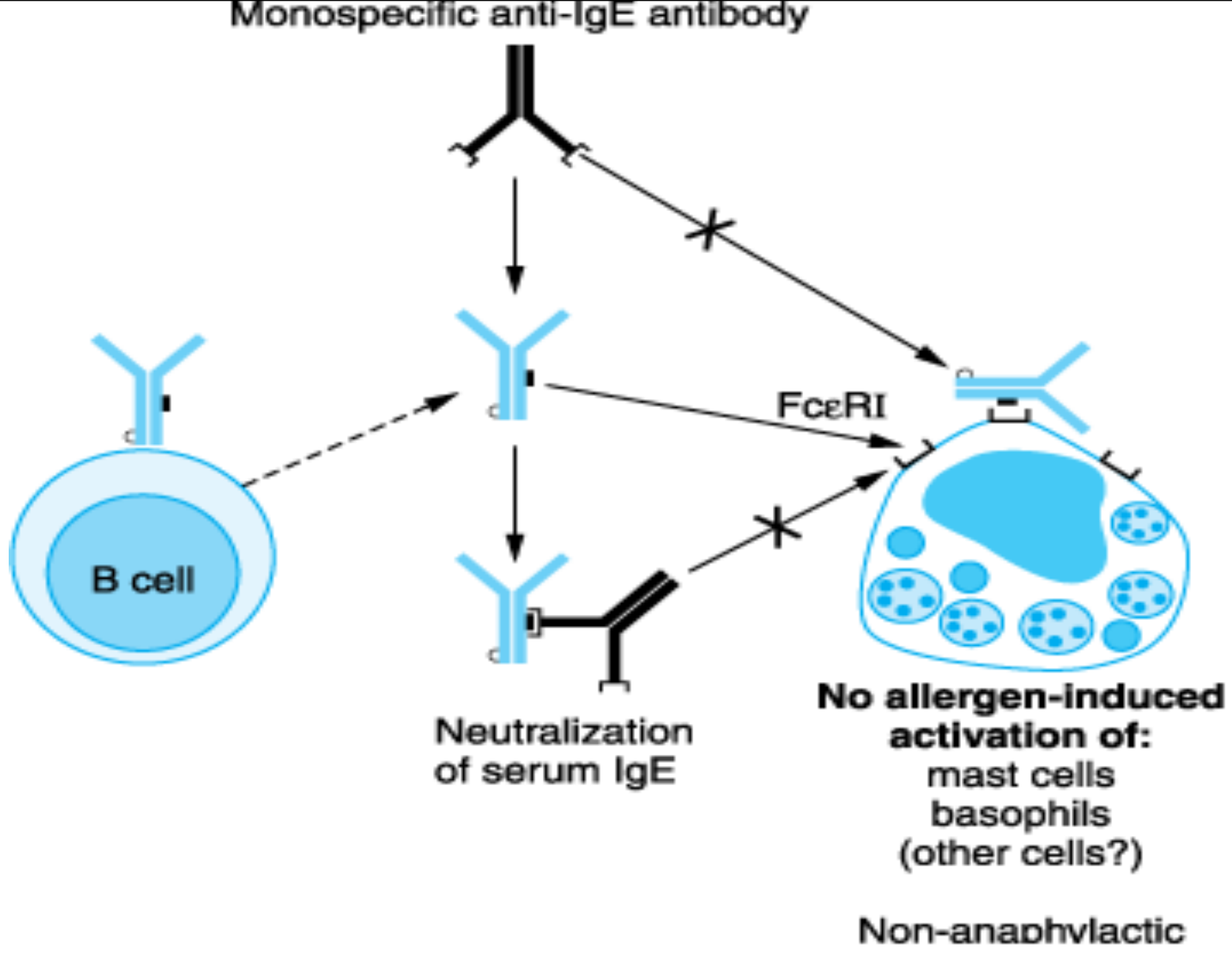
AIDS, cancer patients can't tolerate corticosteroids

- ↓ in nighttime awakenings
- ↓ percent of patients having asthma attacks by 37%
- ↓ need for beta-agonists by 21%

Immunomodulating Biotherapeutics

Omalizumab: Umab = monoclonal antibody

- **It is a humanized monoclonal anti-IgE antibody raised in mice.**
- **Not recognized as foreign by human immune system.**
- **Targeted against the portion of IgE that binds to its receptors (FC-R1 and FC-R2 receptors) on mast cells and other inflammatory cells.**
- **IgE-anti-IgE complexes are cleared from the blood without deposition in the kidneys or joints.**
- **Given as IV or SC injection every 2-4 weeks.**



Source: Brunton LL, Lazo JS, Parker KL: *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 11th Edition: http://www.accessmedicine.com

Immunomodulating Biotherapeutics

- **Monoclonal antibodies directed against cytokines (IL-4, IL-5, and IL-13), antagonists of cell adhesion molecules, protease inhibitors, and immunomodulators aimed at shifting CD4 lymphocytes from the TH2 to the TH1 phenotype or at selective inhibition of the subset of TH2 lymphocytes directed against particular antigens.**

General Therapy of Asthma

- **Oxygen.** When patient has low po2
- **Hydration: Oral or Intravenous.** To loosen the exudate
- **Expectorants.**
- **Antimicrobials.**

Possible Future Therapies

- **There is evidence that asthma may be aggravated—or even caused—by chronic airway infection with *Chlamydia pneumoniae* or *Mycoplasma pneumoniae*. This may explain the reports of benefit from treatment with macrolide antibiotics (erythromycins) .**

Probiotic

- **Feeding *Lactobacillus caseii* to infants born to allergic parents reduced the rate of allergic dermatitis at age 2 years, offers reason for hope.**

Status Asthmaticus

Acute attacks of asthma usually are relived and respond well to treatments but if the attacks are more frequent and repetitive >> status asthmaticus

- **Life threatening exacerbation of asthma symptoms that is unresponsive to standard therapy, preceded by rapid increase in the daily use of bronchodilator drugs.**
- **Provocative factor usually present.**
- **Needs aggressive treatment in the hospital.**

Status Asthmaticus

- **Oxygen.**
- **Inhaled short acting β2 agonists.**
- **Oral or Parenteral corticosteroids.**
- **Subcutaneous β2 agonists.**
- **Inhaled ipratropium maybe effective in some patients**
- **Epinephrine by s.c injection** Life saving measure in anaphylactic shock

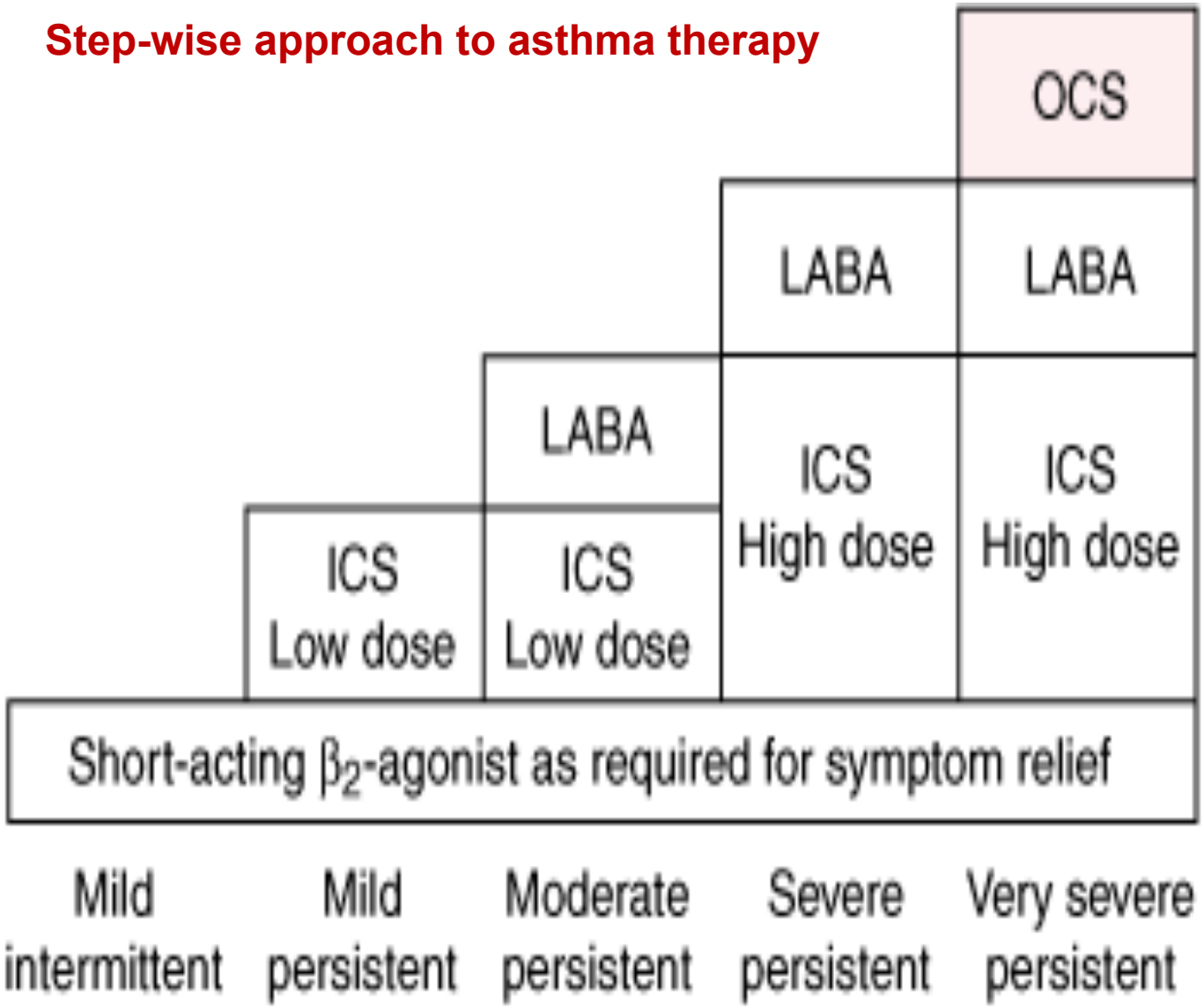
Goal: No deaths on your watch

No patients should die of an acute episode of bronchoconstriction (an asthma attack) at any time, any place.

يعني إذا مات بكون الدكتور حمار (والأعمار بيد الله)

- **Aerosol therapy is available with hand held devices that operate on batteries.**
- **Even more immediate beta-agonist therapy via an "Epi-pen" is readily available.**

Step-wise approach to asthma therapy



Repeated slide from the previous lec

Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

Conclusion

One day, in the future, doctors will know their patient's genetic make-up and response to drugs such that they will be truly able to individualize their patient's therapy on the basis of fact – not guesswork or trial by error.

For now, they should individualize their patient's therapy by therapeutic trial using the lowest dose that works and drugs in rational combinations.

RPL554(Ensifentrine)

Dr skipped the slide

- **A unique inhaled drug, effective and well-tolerated as a bronchodilator, bronchoprotector, and anti-inflammatory drug, in patients with chronic obstructive pulmonary disease (COPD) or asthma.**
- **RPL554 is a dual inhibitor, blocking the activity of 2 phosphodiesterase enzymes: phosphodiesterase 3 (PDE3) and PDE4.**