الجامعة السورية الخاصة
SYRIAN PRIVATE UNIVERSITY

السنة الثالثة

تأثير الأدوية2

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Mechanism of action of sympathomimetic amines in the treatment of asthma

– Activate beta-2 receptors on bronchiolar smooth muscle

- Beta-2 receptor /G-protein complex increases cAMP production
- Increased cAMP activates protein kinase A (PKA)
- PKA phosphorylates myosin light chain kinase (MLCK)
- Phosphorylated MLCK; decreased affinity for $(Ca)_n$calmodulin
- PKA phosphorylates and activates myosin light chain phosphatase (MLCP)
- Less phosphorylation of myosin light chain
- Decreased activity of smooth muscle actin/myosin
- Bronchodilation

Contraindication:

Beta-blockers in asthma

- May precipitate acute attacks in asthmatics
- Antagonize the most effective treatment for an acute attack
- May precipitate asthma in patients not known to be asthmatic
- Selectivity of beta-1 selective antagonists (such as atenolol or metoprolol) is only relative, not absolute

Methylxanthines (xanthines)

- Theophylline (from Thea sinensis) (tea)
- Theobromine (from Theobroma cacao) (chocolate)
- Caffeine (from Caffea arabica, etc.) (coffee)

Xanthine drugs

- Less effective than beta-adrenergics
- Useful to alleviate bronchoconstriction of early and late phase, nocturnal asthma
- Does not relieve hyper-responsiveness

Xanthine pharmacology

- Cellular
  - antagonism of adenosine receptors
  - inhibition of cyclic nucleotide phosphodiesterase

- Systemic
  - CNS stimulation
  - cardiac stimulation
  - diuresis
  - smooth muscle relaxation

Clinical use of **theophylline**

- As a second-line drug, in addition to steroids, in patients whose asthma does not respond adequately to β2-adrenoceptor agonists.
- Intravenously (as **aminophylline**, a combination of theophylline with ethylenediamine to increase its solubility in water) in acute severe asthma.
- Rapid onset of action, can be effective in treating status asthmaticus - usually as an adjunct to an IV or inhaled sympathomimetic, typically albuterol or epinephrine

Theophylline: adverse reactions

- Anorexia
- Nausea & vomiting
- Anxiety
- Fever
- Tremors
- Dehydration
- Seizures
- Cardiac arrhythmias
- Cardiovascular & respiratory collapse

Pharmakinitic of theophylline

- Rapid absorption
- Variable elimination (CYP1A2 and CYP3A4)
- Interaction with
  many other drugs
  smoking
  viral infections
- its plasma concentration is decreased by drugs that induce P450 enzymes (including rifampicin, phenobarbital, phenytoin and carbamazepine).
- The concentration is increased by drugs that inhibit P450 enzymes, such as erythromycin, clarithromycin, ciprofloxacin, diltiazem and fluconaxole.
  and in hepatic insufficiency, heart failure, viral pneumonia,

Clinical use of inhaled muscarinic receptor antagonists

- Anticholinergic agents block vagally mediated contraction of airway smooth muscle and mucus secretion.
- The main compound used as a bronchodilator is **ipratropium.** **Tiotropium** is also available; it is a longer-acting drug used in maintenance treatment of COPD and in patients who are unable to tolerate a SABA.
- For bronchospasm precipitated by β2-adrenoceptor antagonists.
- It has no effect on the late inflammatory phase of asthma.
- The maximum effect occurs after approximately 30 minutes and persists for 3-5 hours. It has few unwanted effects and is, in general, safe and well tolerated. It can be used with β_2-adrenoceptor agonists.

Glucocorticoids

- Corticosteroids inhibit the release of arachidonic acid through phospholipase A2 inhibition, thereby producing direct anti-inflammatory properties in the airways:
  - decreased formation of cytokines, particularly those generated by Th2 lymphocytes
  - decreased activation of eosinophils and other inflammatory cells.
- ICS do not directly affect the airway smooth muscle.
- decrease the inflammatory cascade (eosinophils, macrophages, and T lymphocytes), reverse mucosal edema, decrease the permeability of capillaries, and inhibit the release of leukotrienes.
- After several months of regular use, ICS reduce the hyperresponsiveness of the airway smooth muscle to a variety of bronchoconstrictor stimuli (allergens, irritants, cold air, and exercise).

Glucocorticoids

- ICS are the drugs of choice for long-term control in patients with any degree of persistent asthma.
- Patients who require regular bronchodilators should be considered for glucocorticoid treatment (e.g. with inhaled **beclometasone**).
- More severely affected patients are treated with high-potency inhaled drugs (e.g. **budesonide**).
- Patients with acute exacerbations of asthma may require intravenous **hydocortisone** and oral **prednisolone**.
- A 'rescue course' of oral prednisolone may be needed at any stage of severity if the clinical condition is deteriorating rapidly.
- Prolonged treatment with oral prednisolone, in addition to inhaled bronchodilators and steroids, is needed by a few severely asthmatic patients.

Glucocorticoids

- To be effective in controlling inflammation, glucocorticoids must be used regularly.
- They are given by inhalation (e.g. **beclometasone, Budesonide, Fluticasone, Mometasone**); systemic unwanted effects are uncommon at moderate doses, but oral thrush and voice problems can occur. Systemic effects can occur with high doses. In deteriorating asthma, an oral glucocorticoid (e.g. **prednisolone**) or intravenous **hydrocortisone** is also given.
- Also used as long-acting β2 adrenergic agonist/corticosteroid combination (Formoterol/budesonide, Formoterol/mometasone, Salmeterol/fluticasone)

Precautions when using inhaled steroids

- Confirm objective evidence of the value of this therapy which tends to decrease compliance with other aerosol usage
- Standard dosing (2-4 puffs, 2-4 times per day) should not be exceeded
- Use a spacer; monitor to minimize oral thrush and laryngeal dysfunction
- ICS can cause oropharyngeal candidiasis (due to local immune suppression). Patients should be instructed to rinse the mouth in a "swish-and-spit" method with water following use of the inhaler to decrease the chance of these adverse events.

Systemic side effects of chronic glucocorticoids

- ↑ gluconeogenesis (liver)--hyperglycemia
- ↑ release of amino acids-catabolism (muscle)--muscle weakness
- ↑ release of fatty acids-lipolysis (fat)--together with increase in insulin, leads to inappropriate fat deposition, obesity
- ↑ bone resorption--leading to osteoporosis, fractures
- ↑ fibroblast proliferation--thin skin, poor wound healing
- ↓ collagen synthesis
- ↓ growth (in children)
- ↓ changes in mood and excitability--euphoria, restlessness

altered leukocyte functions (anti-inflammatory)--may mask underlying symptoms

suppression of the HPA axis: acute withdrawal can lead to death

Precautions when using oral steroids

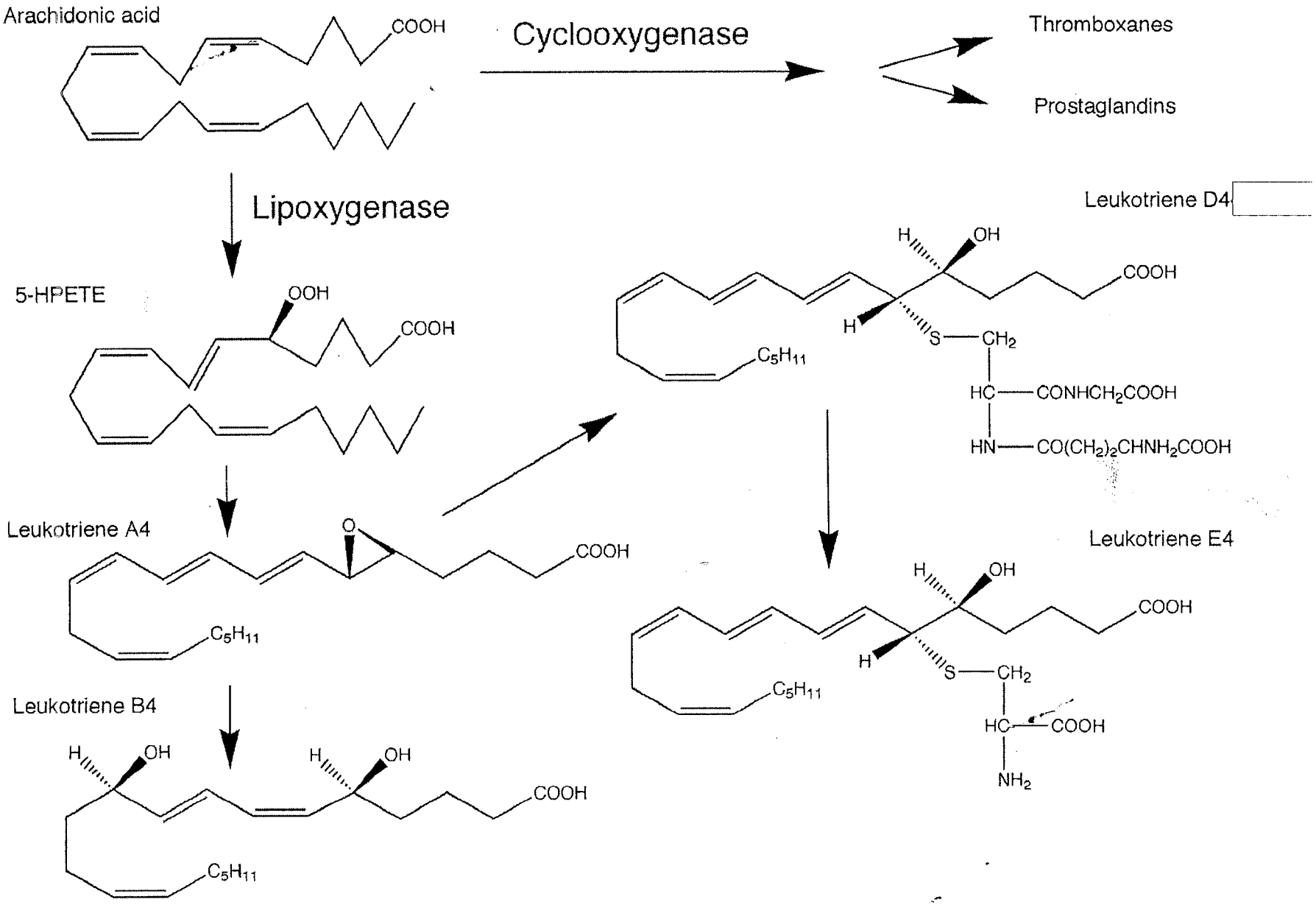
- Reduce to lowest daily or alternate day dosage as soon as symptoms allow
- Monitor for hypertension, diabetes, weight gain, mental changes, infections, skin thinning, osteoporsis - administer prophylactic calcium
- Monitor FEV1 for 2 weeks to establish objective evidence of benefit
- Repeatedly evaluate patient to determine if steroid therapy can be discontinued.....

Treatment of Asthma

Controller drugs:
prevent asthma attacks and/or reduce severity

- **Bronchdilators:**
  - Certain sympathomimetics (e.g., salmeterol)
  - Methylxanthines (theophylline)
  - Muscarinic receptor antagonists
- **Anti-inflammatory agents**
  - Corticosteroids
  - **Leukotriene synthesis inhibitors (zileuton)**
  - Leukotriene antagonists (zafirlukast)
  - Cromoglicate and nedocromil
  - Histamine H_1-receptor antagonists
  - Antibodies

Arachidonic acid metabolism

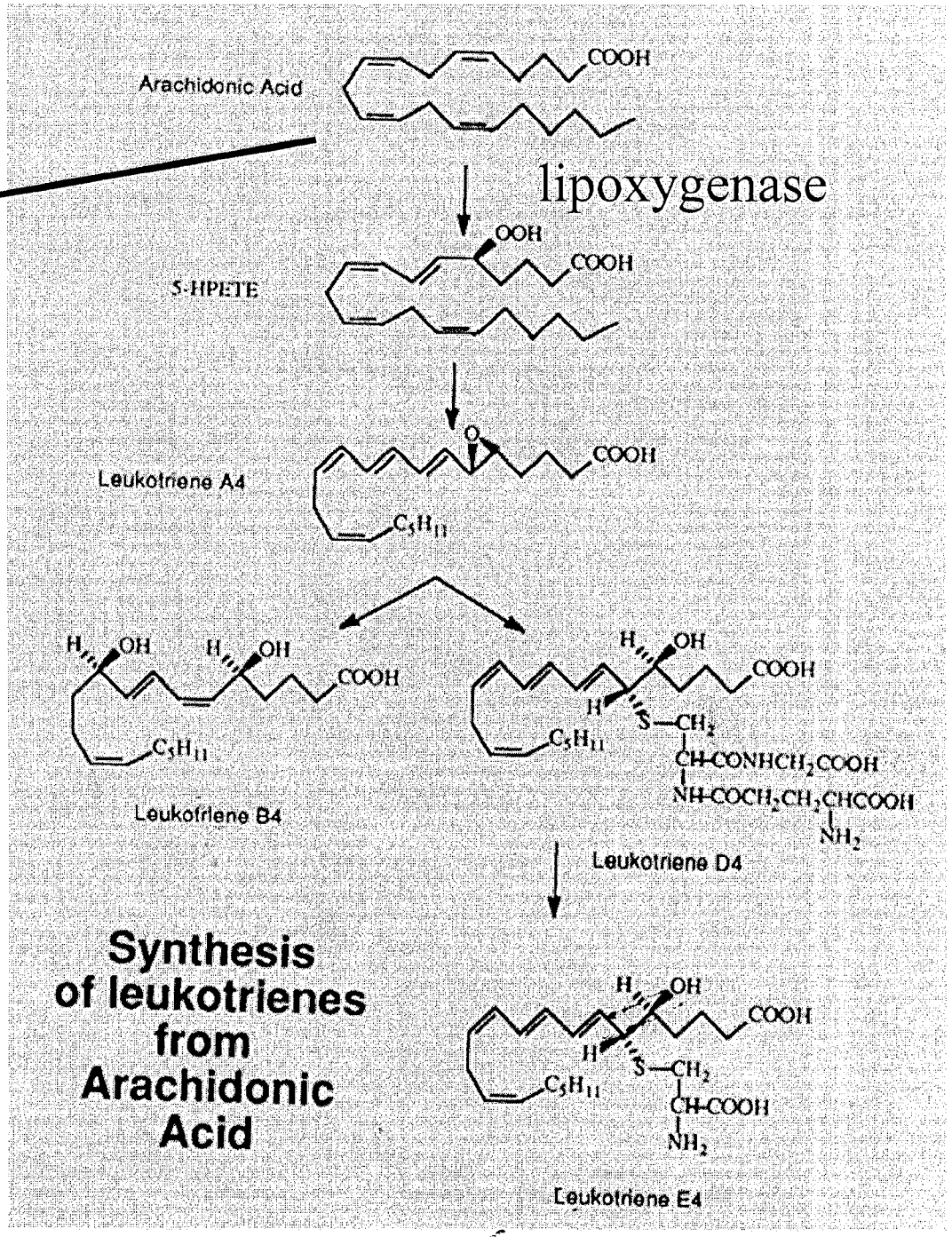


NSAIDS

cyclooxygenase

thromboxanes

prostaglandins

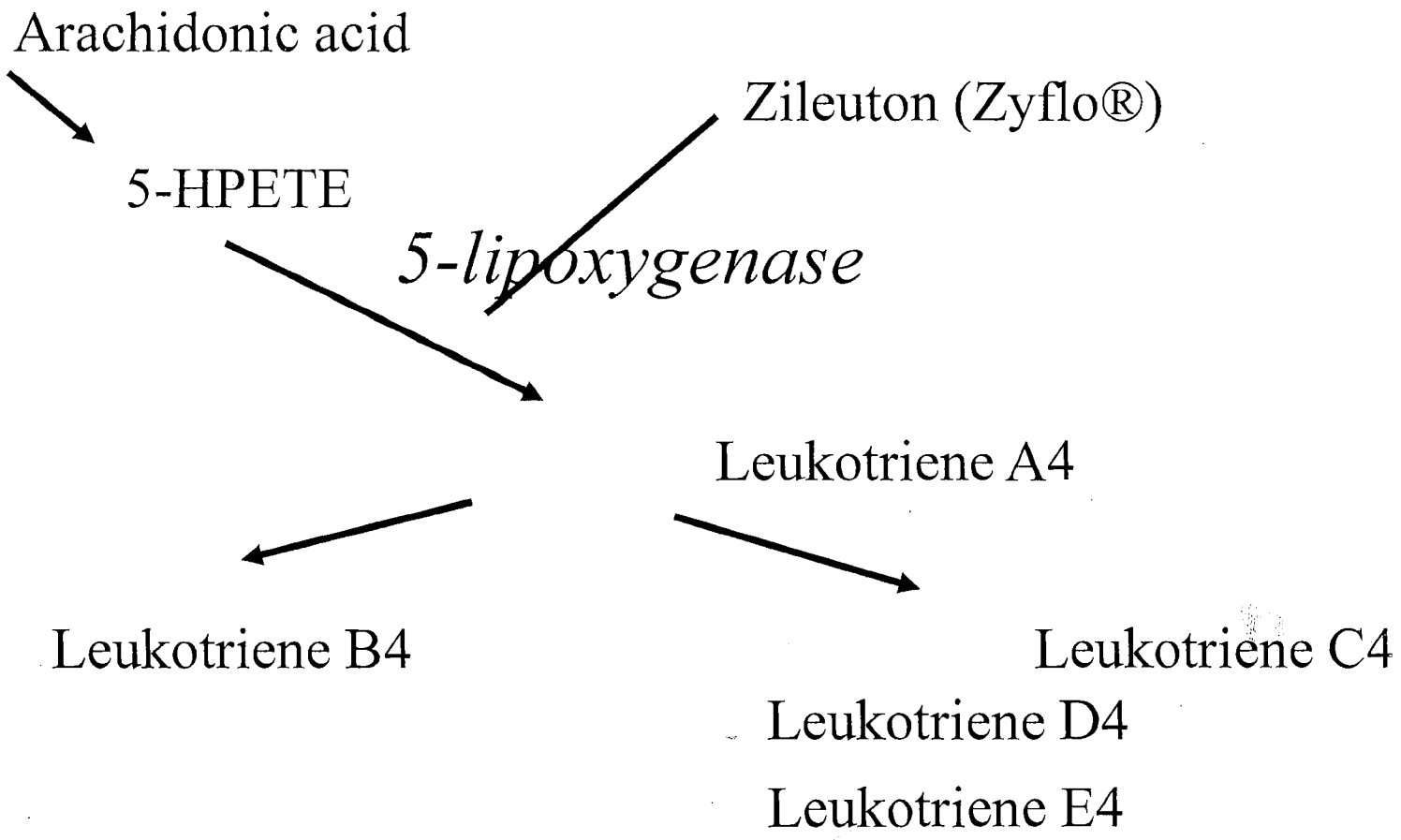


Zileuton: Mechanism of Action

- Zileuton (Zyflo®) is a highly selective inhibitor of 5-lipoxygenase
- Inhibits the synthesis of leukotrienes (LTB_4, LTC_4^*, LTD_4^* and LTE_4) - potential for application in a variety of inflammatory diseases (e.g., colitis, rheumatoid arthritis) - but currently only approved for asthma

- Very short half life (~1-2 hours), given QID

Leukotrienes and asthma



LTB4 receptor
chemotaxis, immunomodulation

LT receptor ($CYSLT_1$)
bronchoconstriction, mucus secretion,
hyperresponsiveness, eosinophilia

Zileuton (Zyflo®)

- Indicated for chronic treatment of asthma. Should be taken even during symptom-free periods. **Zileuton is NOT a bronchodilator** - it **should NOT be used to treat acute episodes of asthma**.
- Reassess therapy if short-acting bronchodilators are needed more often than usual
- Monitor patients on a regular basis - the most serious adverse reaction is elevation of liver enzymes.

Treatment of Asthma

Controller drugs:
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- **Anti-inflammatory agents**
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  - Leukotriene synthesis inhibitors (zileuton)
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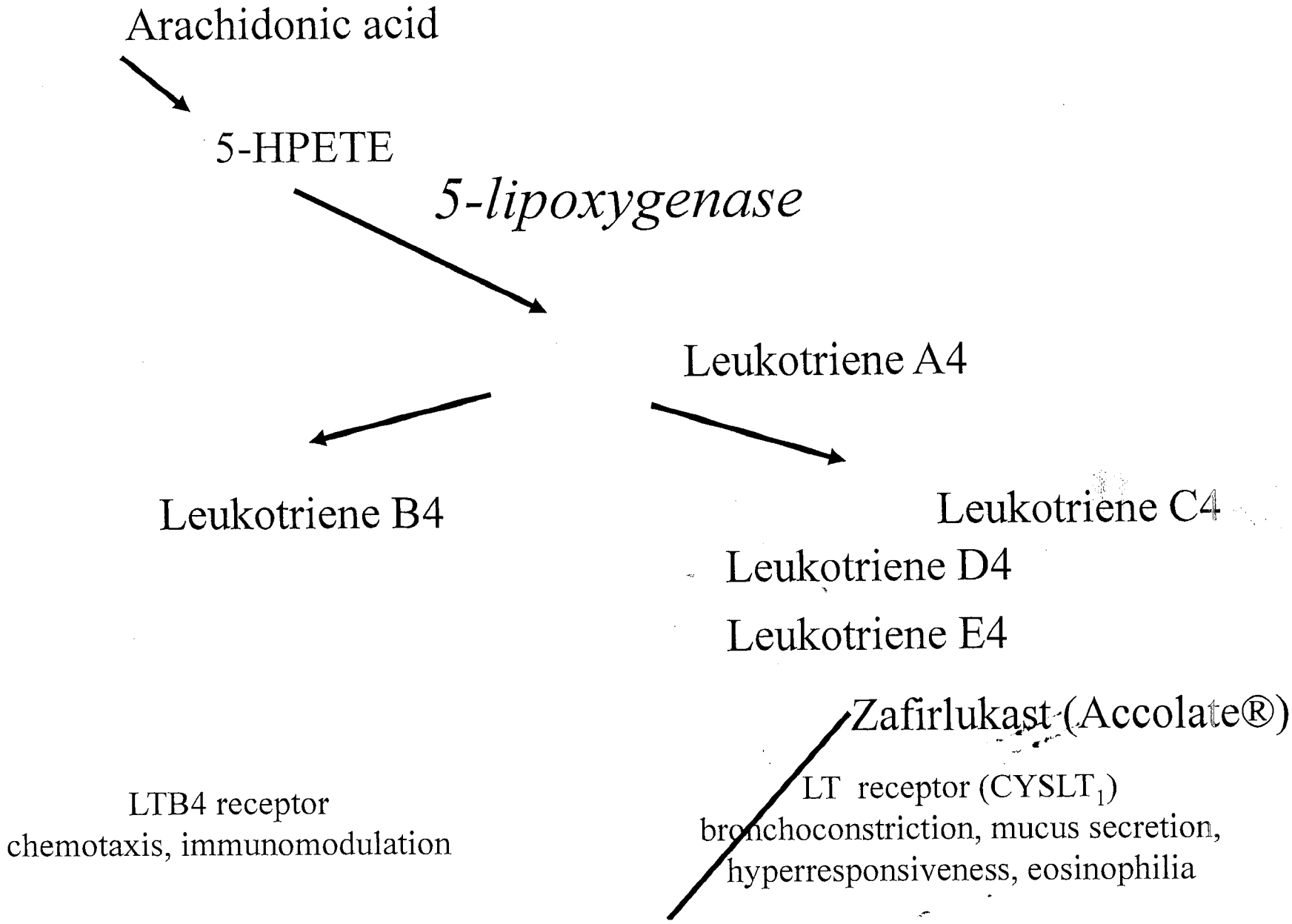
Mechanism of Action

- Third-line drugs for asthma.
  - Competitively antagonise cysteinyl leukotrienes at CysLT1 receptors are used mainly as add-on therapy to inhaled corticosteroids and long-acting β2 agonists
- Montelukast , Zafirlukast (Accolate®) are selective and competitive receptor antagonists of leukotrienes D4 and E4

Leukotrienes and asthma



Zafirlukast: Selected adverse reactions

Adverse Event	Zafirlukast (n=4058)	Placebo (n=2032)
Headache	12.9%	11.7%
Nausea	3.1%	2.0%
Vomiting	1.5%	1.1%
Diarrhea	2.8%	2.1%
Dizziness	1.6%	1.5%
SGPT elevation	1.5%	1.1%

- Disodium **cromoglycate** (cromolyn sodium, Intal®, Nasalcrom®)
- **Nedocromil** (Tilade®)

- Prophylactic anti-inflammatory agents
- Inhaled as a nebulized solution
- Inhibit mast cell degranulation and the release of histamine
- Alternative therapy for mild persistent asthma. However, not useful in managing an acute asthma attack, because they are not a bronchodilator.
- Due to there short duration of action, these agent requires dosing three or four times daily, which affects adherence and limits its use.
- Adverse effects are minor and include cough, irritation, and unpleasant taste.

Histamine H1-receptor antagonists

- Although mast cell mediators play a part in the immediate phase of allergic asthma and in some types of exercise-induced asthma, histamine H1-receptor antagonists **have no routine place in therapy,** although they **may be modestly effective in mild atopic asthma**, especially when this is precipitated by acute histamine release in patients with concomitant allergy such as severe hay fever.

Anti-IgE treatment

- **Omalizumab** is a humanised monoclonal anti-IgE antibody. It is effective in patients with allergic asthma as well as in allergic rhinitis. It is of considerable theoretical interest, but it is very expensive and its place in therapeutics is still unclear.

Severe Acute Asthma (Status Asthmaticus)

Severe acute asthma is a medical emergency requiring **hospitalisation**. Treatment includes:

- **oxygen** (in high concentration, usually 60%)
- inhalation of **salbutamol** given by nebuliser
- intravenous **hydrocortisone**
- followed by a course of oral **prednisolone**.
- Additional measures occasionally used include nebulised **ipratropium**, intravenous **salbutamol** or **aminophylline**, and **antibiotics** (if bacterial infection is present).

Drug list for asthma

- * acetylcholine
- * albuterol (Proventil®, Ventolin®)
- * aminophylline (theophylline ethylenediamine)
- * beclomethasone dipropionate (Vanceril®)
- * disodium cromoglycate cromolyn sodium (Intal®)
- * epinephrine (Adrenalin®
- * ipratropium (Atrovent®)
- * isoproterenol (Isuprel®)
- * nedocromil (Tilade®)
- * prednisone (Deltasone®)
- * salmeterol (Serevent®)
- * terbutaline (Brethaire®, Brethine®, Bricanyl®)
- * theophylline (Theo-Dur®, Slo-Phyllin®, Somophyllin-T®, Somophyllin CRT®, Theobid®)
- * triamcinolone acetonide (Azmacort®)
- * zafirlukast (Accolate®)
- * zileuton (Zyflo®)