Drugs used in allergic disorders
(asthma and allergic rhinitis)
Chest x-ray
Obr. 10.1. Schematický řez bronchiální stěnou:
A – na úrovni průdušnice a průdušek;
B – na úrovni bronchiolů.
CC = ciliární epitelová buňka; GC = pohárová buňka; BM = bazální membrána; BC = bazální buňka;
SM = hladká svalovina; MG = hlenová žlázka; CA = chrupavka; CL = Clarova buňka
Asthma - definition

- Asthma is chronic inflammatory airway disease
- The cells involved in pathogenesis are: eosinophilic granulocytes, mast cells, to the less extend neutrophilic a bazophilic granulocytes.
- This inflammation increases airway hyperreactivity resulting in reversible bronchial obstruction
- This dissolves either spontaneously or after treatment
Asthma is lung disease characterized by:

1. Reversible airway obstruction (not always complete) which can be influenced by means of or without treatment
2. Airway inflammation
3. Airway hyperreactivity
Asthma - pathophysiology

Dysfunction
(Smooth muscles)

Inflammation
(Airways)

Remodelation
(Airways)
Grass pollen
Grass pollen
Pollen grain
Mould
Seasonal occurrence of major allergens

- Plane tree
- Grasses
- Alternaria
- Cladosporium
- Aspergillus

The graph illustrates the seasonal occurrence of major allergens, showing peaks in different months for each allergen.
Mite
Bronchoconstriction

Before

10 minutes after allergen trigger

P Howarth
Airway mucosal edema
Epithelial disruption

Asthma and mediators

• Bronchial hyperreactivity is a result of permanent inflammation induced by means of various triggers - allergens, viruses, chemicals, etc.

• Inflammatory mediators are released from the cells - eosinophiles, neutrophiles, monocytes, mastocytes, macrophages.
  – Histamine is pre prepared
  – Other mediators are metabolites of arachidonic acid
    • Cyclooxygenase- PGD$_2$
    • Lipooxygenase - leucotriens
    • PAF
Mediators

Mast cell granule

Arachidonic acid

Membrane Phospholipid

IgE

Antigen

Preformed substances from mast cell granules:
- Histamine
- Neutral proteases
- Acid hydrolases
- Heparin proteoglycan
- ECF-A
- NCF

Cyclo-oxygenase pathway

Leukotriene $B_4$

5-Lipoxygenase pathway

Leukotriene $A_4$

Thromboxanes

Prostaglandins

Prostacyclin

Leukotriene C$_4$

Leukotriene D$_4$

Leukotriene E$_4$

Slow-reacting substance of anaphylaxis (SRSA)
Immediate and late allergic reaction
Asthma - epidemiology

- Prevalence - 3 - 10 %
- Predominantly outpatient treatment
- Frequent underestimation of the diagnosis may bias epidemiological data
Age prevalence of asthma
Asthma – treatment objectives

• Maintain normal activity (including exercise and sports)
• Maintain lung function close to normal values
• Prevent problems (cough, dyspnoea)
• Prevent exacerbations
• Prevent AE linked to therapy
Asthma – treatment (management)

- Patient’s education
- Environmental control
- Pharmacotherapy
- Functional monitoring
Asthma - pharmacotherapy

- Antiasthmatics
  - Bronchodilators
    - $\beta_2$-adrenomimetics
    - Theophylline
    - Anticholinergics
  - Anti-inflammatory agents
    - Cromons
    - Glucocorticoids
    - Antileukotriens
Antiasthmatics - application routes

Inhaled

• Particle size 2 - 5 μ
  - MDI – metered dose inhaler (spray)
  - MDPI – metered dose powder inhaler
  - spacers – large volume containers (to improve inhalation)

• Used for: corticosteroids, β₂-agonists, cromons, anticholinergics

• Infrequent AE
Inhaled drug disposition
MDI
(CFC free)
Spiral insertion for degrading of drug aggregates

Inhalation channel
Scraper
One metered dose
Drug reservoir
Rotating dosing disc

Figure 16.8 Turbuhaler (Astra).
MDPI - ...disk
Spacers
Deposition pattern of inhaled antiasthmatic drug
Deposition pattern poor technique
Antiasthmatics - application routes

Oral

- Theophylline – only long acting glucocorticoids, $\beta$-agonists
- To gain equal effect as in inhaled application 20 x higher dose is required
- Systemic AE frequent
$\beta_2$-agonists
### β-agonists – classification according to specificity

<table>
<thead>
<tr>
<th></th>
<th>$\alpha_1$</th>
<th>$\alpha_2$</th>
<th>$\beta_1$</th>
<th>$\beta_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>noradrenaline</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>adrenaline</td>
<td>++</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>isoprenaline</td>
<td>-</td>
<td>-</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>clonidine</td>
<td>-</td>
<td>+++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>salbutamol</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>terbutaline</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>dobutamine</td>
<td>-</td>
<td>-</td>
<td>+++</td>
<td>+</td>
</tr>
</tbody>
</table>
β-agonists – structure

- Adrenomimetic molecule carries 3 important sites influencing efficacy
  - Group on N side chain (radical size influencing affinity)
  - OH on C1 side chain
  - OH in meta and para position (3 and 4) (OH substitution influencing intrinsic activity)
β-agonists– structure

Catecholamine prototype
**β-agonists – mode of action**

- **β-mimetic receptor**
- **membrane**
- **adenylatcyclase**
- **phosphodiesterase**
- **methylxantins**
- **AMP**
- **Proteinkinase activation**
- **reaction**

- **ATP**
- **cAMP**
### β-agonists – classification according to selectivity

<table>
<thead>
<tr>
<th></th>
<th>( \beta_2 )</th>
<th>( \beta_1 )</th>
<th>( \beta_2 : \beta_1 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>isoprenaline</td>
<td>1,0</td>
<td>1,0</td>
<td>1,0</td>
</tr>
<tr>
<td>fenoterol</td>
<td>0,6</td>
<td>0,005</td>
<td>120,0</td>
</tr>
<tr>
<td>formoterol</td>
<td>20,0</td>
<td>0,05</td>
<td>400,0</td>
</tr>
<tr>
<td>salbutamol</td>
<td>0,55</td>
<td>0,0004</td>
<td>1375,0</td>
</tr>
<tr>
<td>salmeterol</td>
<td>8,5</td>
<td>0,0001</td>
<td>85000,0</td>
</tr>
</tbody>
</table>
\( \beta_2 \)-agonists – AE

- Muscular tremor (in higher doses)
- Palpitation
- Headache
- Paradoxal bronchospasms (in inhaled forms)
- In rare cases allergy
### Topic (inhalation) $\beta_2$-agonists

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terbutaline</td>
<td>Bricanyl</td>
</tr>
<tr>
<td>Fenoterol</td>
<td>Berotec</td>
</tr>
<tr>
<td>Formoterol</td>
<td>Foradil, Atimos, Forair, Formovent …</td>
</tr>
<tr>
<td>Salbutamol</td>
<td>Ventolin, Ventodisc</td>
</tr>
<tr>
<td>Salmeterol</td>
<td>Serevent</td>
</tr>
<tr>
<td>Prokaterol</td>
<td>Alvesco</td>
</tr>
</tbody>
</table>
Systemic (p.o., i.v.) $\beta_2$-agonists

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terbutaline</td>
<td>Bricanyl</td>
</tr>
<tr>
<td>Klenbuterol</td>
<td>Spiropent</td>
</tr>
<tr>
<td>Prokaterol</td>
<td>Lontermin</td>
</tr>
</tbody>
</table>
Theophylline
Theophylline

- **Mode of action**
  - Probably competitive inhibition adenosine receptors.
  - Theophylline structure is close to adenosine.
  - This effect can be observed in therapeutic concentrations.
  - Phosphodiesterase inhibition NOT
  - Therapeutic concentration is 5 – 20 µg/L
Theophylline

- Narrow therapeutic window: 5 – 20 μg/l
- Serum levels monitoring needed
- Large variability in clearance due to hepatic metabolism (cytochrome P 450 CYP 3A4)
Increased theophylline clearance

• Enzyme induction
  - rifampicin
  - phenobarbital
  - ethanol
• Tobacco and marijuana smoking
• Age 1 - 16 years
Decreased theophylline clearance

- Enzyme inhibition
  - cimetidine
  - erythromycin, some fluoroquinolones
  - allopurinol
- Impaired liver function
- Infection, vaccination
- Age
Theophylline – summary

- Additive effects with $\beta$-agonists
- Only sustained release forms
- Frequent interactions and AEs
## Theophylline containing drugs

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
</tr>
</thead>
<tbody>
<tr>
<td>Theophylline</td>
<td>Aflonilum SR, Euphyllin CR, Teotard, Teoplus, Spophyllin retard</td>
</tr>
<tr>
<td>Aminofilin</td>
<td>Aminophyllinum retard, Syntophyllin</td>
</tr>
</tbody>
</table>
Anticholinergics

• Mode of action
  - competitive inhibition of postsynaptic cholinergic receptor on vagal nervous ending
Anticholinergics

- Lower efficacy than $\beta$-agonists
- Additive effect with $\beta$-agonists
- Possible replacement of theophylline
  - Ipratropium
  - Thiotropium (CHOPN)
## Anticholinergics

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipratropium</td>
<td>Atrovent</td>
</tr>
<tr>
<td>Thiotropium</td>
<td>Spiriva</td>
</tr>
</tbody>
</table>
Cromons
Cromons

• Mode of action
  – Prevent mast cells degranulation
  – Active also in late phase of allergic reaction in other cells
  – Advantage in pediatrics
  – Nedocromil – brand: Tilade
Glucocorticoids
Glucocorticoids

Mineralocorticoid pathway

Glucocorticoid pathway

Sex hormone pathway

Cholesterol

Aminoglutethimide

ACTH

Angiotensin II

Trilostane

3-β-dehy.

21-β-hydrox.

11-β-hydrox.

17-α-hydrox.

17-α-hydroxyprogesterone

17-α-Hydroxypregnenolone

Pregnenolone

Progesterone

11-Deoxycorticosterone

11-Deoxycortisol

Androstenedione

Testosterone

Oestradiol

Oestrone

Oestriol

Dehydroepiandrosterone

3-β-dehy.
Cortisol

- Synthesis: in adrenals - zona fasciculata and reticularis
- Daily production 20 mg
- Circadian rhythm ACTH
- CBG ($\alpha_2$-globulin) - 75% and albumin - 5%, 20% free
- Saturation CBG 20-30\(\mu\)g/dl
- Synthetic glucocorticoids predominantly bound to albumin
From cortisol to synthetic steroids (I)

cortisol
betamethason
other variations
From cortisol to synthetic steroids (II)

beclomethasone
(flufticason)
Glucocorticoids - regulation

hypothalamus

CRF

pituitary

ACTH

adrenal cortex

glucocorticoids

exogen ACTH

exogen CS

Metyrapon

(β-hydroxylation inhib. on C11 cortizol)
target tissue
Glucocorticoids

• Mode of action

- General anti-inflammatory effect, inflammatory cells flux and inflammatory mediators release inhibition.
- Lipocortin induction - decrease in PDE, PAF and arachidonic acid concentration
Mode of action (I)

1. Entry into cell
2. Binding to GR
3. Hormone - receptor complex, after activation - dimmer – transport to nucleus
4. Interaction on gene and regulatory proteins level - GRE (transcriptional mechanisms)
5. Without hormone – inhibition of receptor protein
6. Fast feed back (nontranscriptional) on membrane level
Mode of action (II)

*GRE encoded: GGTACA nnn TGGTCT
Glucocorticoid receptor (I)
Glucocorticoid receptor (II)
Glucocorticoid receptor (III)

- GR belongs to superfamily of structural proteins (nuclear receptors) transducing signals from small lipophillic molecules (D vitamin, retinoids, glucocorticoids, thyroid hormones)
- Structure of GR:
<table>
<thead>
<tr>
<th></th>
<th>receptor affinity (mg/l)</th>
<th>intrinsic activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisolone</td>
<td>2.60</td>
<td>1.0</td>
</tr>
<tr>
<td>BDP (BMP)</td>
<td>0.03</td>
<td>86.7</td>
</tr>
<tr>
<td>Flunisolide</td>
<td>0.22</td>
<td>11.8</td>
</tr>
<tr>
<td>Triamcinolone acetonide</td>
<td>0.20</td>
<td>13.0</td>
</tr>
<tr>
<td>Budesonide</td>
<td>0.04</td>
<td>65.0</td>
</tr>
<tr>
<td>Fluticason propionate</td>
<td>0.02</td>
<td>130.0</td>
</tr>
</tbody>
</table>

Derendorf, 1998
Glucocorticoid receptor (V)

Relative affinity

- Deka
- B17-m
- BUD
- FP
Glucocorticoids and asthma

- Inhalation form (MDI, MDPI)
- Oral form to respect circadian rhythms (morning - peak)
- Parenteral form only in severe cases
Inhalation glucocorticoids

- Patient exposed to low dose
- Minimum effect on HPA axis
- Practically no influence on growth
- Almost lack of systemic effect
- Local candidosis
Result of steroid therapy

before

after

P Howarth  Berlin 1999
# Topical (inhalation) steroids

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclometason</td>
<td>Aldecin, Becotide, Becodisc, Becloforte</td>
</tr>
<tr>
<td>Budesonid</td>
<td>Budair, Inflammide, Miflonid, Pulmicort, Pulmax ...</td>
</tr>
<tr>
<td>Flutikason</td>
<td>Flixotide</td>
</tr>
<tr>
<td>Mometason</td>
<td>Asmanex</td>
</tr>
<tr>
<td>Ciklesonid</td>
<td>Alvesco</td>
</tr>
</tbody>
</table>
## Inhalation combinations with $\beta_2$-agonists

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fenoterol + ipratropium</td>
<td>Berodual</td>
</tr>
<tr>
<td>Salmeterol + fluticason</td>
<td>Seretide</td>
</tr>
<tr>
<td>Formoterol + budesonid</td>
<td>Symbicort</td>
</tr>
</tbody>
</table>
Antileucotriens
Leucotriens and antileucotrienes

• In asthma
  – Bronchoconstriction
  – Stimulate mucus secretion
  – Contribute to airway obstruction

• Antileucotriens may modify inflammation in various diseases

• Anti-inflammatory effect of antileucotrienes is utilised in asthma
Antileucotriens

• Competitive leucotrien receptor antagonists (LTRA)
  – montelucast, zafirlucast, pranlucast, pobilucast, verlucast ...

• Leukotrien synthesis inhibitors (LTSI)
  – 5-lipooxigenase inhibitors (5-LO): zileuton
  – 5-lipooxigenase activating protein inhibitor (FLAP)
## Asthma and antileucotrienes (I.)

<table>
<thead>
<tr>
<th></th>
<th>Broncho constriction</th>
<th>Early response</th>
<th>Delayed response</th>
<th>Excercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>zafirlukast</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>pranlukast</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>montelukast</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>poblukast</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>zileuton</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
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</table>
# Asthma and antileucotrienes (II.)

<table>
<thead>
<tr>
<th></th>
<th>Hyper sensitivity</th>
<th>cold</th>
<th>NSAID</th>
<th>chronic</th>
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<tbody>
<tr>
<td>zafirlukast</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>pranlukast</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>montelukast</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>pobrilukast</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>zileuton</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>
## Antileucotriens

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zafirlucast</td>
<td>Accolate</td>
</tr>
<tr>
<td>Montelucast</td>
<td>Singulair</td>
</tr>
</tbody>
</table>
Omalizumab (Xolair)

- Recombinant humanized Mab, with selective binding to human immunoglobulin E (IgE).
- Reduces amount of free IgE, responsible for the initiation of allergic cascade.
- Indication – only for patients with asthma caused by IgE
PEF evaluation

Admission to hospital with acute attack

Graph showing peak flow (L/min) over days.
COPD pharmacotherapy

- Anticholinergics
- Selective $\beta_2$-agonists
- Methylxanthins
- PDE4 inhibitors
- Glucocorticoids
- Oxygenoterapy
Roflumilast: PDE4 inhibitor influencing systemic and lung inflammation connected with CHOPN.

Mode of action: PDE4 inhibition (main enzyme metabolizing cAMP)

Indication: maintenance therapy of severe COPD (FEV1 after bronchodilators less than 50 % of appropriate value)
Allergic rhinitis
Allergic rhinitis

**Intermittent symptoms**
- <4 days per week
- or <4 weeks

**Persistent symptoms**
- >4 days/week
- and >4 weeks

**Mild**
- normal sleep
- normal daily activities, sport, leisure
- normal work and school
- no troublesome symptoms

**Moderate-Severe**
- one or more items
  - abnormal sleep
  - impairment of daily activities, sport, leisure
  - problems caused at work or school
  - troublesome symptoms
Pharmacotherapy

- Local decongestives
- Antihistaminics
- Cromons
- Anticholinergics
- Corticoids - locally
- Corticoids - systemic
Local decongestives

- Main effect - decongestion, vasoconstriction,
- Long term effect - hypoxia - chronic mucosal changes
# Topical nasal decongestives

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fenylefrin</td>
<td>Vibrocid</td>
</tr>
<tr>
<td>Nafazolin</td>
<td>Sanorin</td>
</tr>
<tr>
<td>Nafazolin + antazolin</td>
<td>Sanorin - analergin</td>
</tr>
<tr>
<td>Oxymetazolin</td>
<td>Nasivin</td>
</tr>
<tr>
<td>Tetryzolin</td>
<td>Tyzin</td>
</tr>
<tr>
<td>Xylometazoline</td>
<td>Otrivin, Olynth, Nasenspray AL</td>
</tr>
</tbody>
</table>
Cromons

• DSSG
  – Mast cells stabilization, prevents degranulation
  – Application: 4 - 6 x day locally
**Anticholinergics**

Ipratropium bromide

- Acetylcholine release inhibition
- Suppression of mucus secretion
- Application: 3 x day locally
<table>
<thead>
<tr>
<th>Category</th>
<th>Generic</th>
<th>Brand</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasal cromons</td>
<td>Na cromoglycate</td>
<td>Allergocrom, Allergo-comod, Cromobene, Cromohexal</td>
</tr>
<tr>
<td>Nasal anticholinergics</td>
<td>ipratropium bromide</td>
<td>Atrovent</td>
</tr>
<tr>
<td>Antileucotriens</td>
<td>montelukast, zafirlukast</td>
<td>Singulair, Accolate</td>
</tr>
</tbody>
</table>
Antihistaminics – 1st generation

- Histamine H₁ receptor antagonists (non selective)
- Sedative effect
- Antiemetic effect
- Muscatine receptor affinity (anticholinergic activity)
Antihistaminics – 2nd generation

- Selective action - no sedative effect
- Mediator synthesis and release inhibition
  - mast cells, monocytes and basophiles
  - prostaglandin and leucotrien suppression
- Suppression of eosinophils migration, chemotaxis and their endothelial adhesion
Antihistaminics – 2nd generation

• Advantages
  • Onset of action
  • Long term effect
  • Active metabolites
  • Good compliance
  • Systemic effects (ocular, dermal)

• Disadvantages
  • Adverse events: weight gain (*astemizol*)
  • Myocardium - QT interval (*terfenadin*)
  • Hepatotoxicity
  • Drug interactions e.g. Macrolides, azole antimycotics
# Antihistaminics – 2nd generation

<table>
<thead>
<tr>
<th></th>
<th>Generic</th>
<th>Brand</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systemic</strong></td>
<td>Cetirizin</td>
<td>Alerid, Cetirizin-SL, Letizen, Zodiac, Zyrtec, Claritin, Flonidan, Loratadin-SL, Lotanax</td>
</tr>
<tr>
<td></td>
<td>Loratadin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Terfenadin</td>
<td></td>
</tr>
<tr>
<td><strong>Topical</strong></td>
<td>Azelastin</td>
<td>Allergodil</td>
</tr>
<tr>
<td></td>
<td>Levocabastin</td>
<td>Livostin</td>
</tr>
<tr>
<td><strong>Immunomodul. effect</strong></td>
<td>Desloratadin</td>
<td>Aerius</td>
</tr>
<tr>
<td></td>
<td>Levocetirizin</td>
<td>Xyzal</td>
</tr>
</tbody>
</table>
## FDC

(antihistaminics + decongestives)

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loratadin + pseudoefedrin</td>
<td>Clarinase</td>
</tr>
<tr>
<td>Fenyramin + pseudoefedrin</td>
<td>Disophrol</td>
</tr>
<tr>
<td>Carbinoxamin + fenylefrin</td>
<td>Rhinopront</td>
</tr>
</tbody>
</table>
# Topical nasal steroids

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
</tr>
</thead>
<tbody>
<tr>
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# Treatment of nasal symptoms

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SIT: specific immunotherapy

For sublingual and nasal SIT, the recommendation is only for very high dose treatment.