GIT PHARMACOLOGY
When it is necessary to intervene?

- **motility disorders** (vomiting, reflux disease, disorders of passages, irritant colon, colics)
- **absorption disorders** (disorders of enzymes secretion, disorders of the absorption)
- **peptic lesions** (ulcer disease GD)
- **inflammatory bowel disease** (ulcerative colitis, Crohn disease)
- **excessive intake of food** (antiobesitics)
- **haemorrhage in GIT** (prophylaxis and treatment)
Nausea and vomiting

- **nausea** – only subjective symptom
- **vomiting** -
  - *metabolic disorders* (loss of potassium, water, HCl),
  - *aspiration, mucosal defects*
- the need for prevention and treatment
- of importance especially in oncology
antiemetics
Nausea and vomiting - regulation

**Vomiting center** (medulla oblongata)

*Beware:* *is not protected by the HE barrier – easy penetration of toxins!*

**signaling:** afferent neuronal pathways
- from GIT and other tissue (stomach, myocardium)
- from CNS (psychogenic stimulation, intracranial hypertension)
- from vestibular apparatus (Menier dis., kinetosis, motion sickness)
  - aferentní humoral stimulatons
- toxins (bacterial, uremia), drugs (cytostatics, digoxin, morphine), endocrine disorders (gravidity)
Nausea and vomiting - regulation

**Chemoreceptors**
- alcohol, emetics,
- cytotoxix drugs,
- irradiation, gravidity

**Vomiting center**
- larynx, stomach
  - mechanical and chemical stimulation

**Cortex**
- psych. stimulation
- migraine

**Vestibular apparatus**
- motion, hyperstimulation
Nausea and vomiting regulation

- mediators

chemoreceptors
- mediator: dopamin, serotonin

Vomiting centre
- mediator: acetylcholin

Larynx, stomach
- mediator: serotonin, histamin

cortex
- mediator: acetylcholin

vestibullar apparatus
- mediator: histamin, acetylcholin
Nausea and vomiting regulation

- mediators
  
  chemoreceptors
  mediator: dopamin, serotonin

  cortex
  mediator: acetylcholin

  vestibular apparatus
  mediator: histamin, acetylcholin

  larynx, stomach
  mediator: serotonin, histamin

  vomiting centre
  mediator: acetylcholin

  dopaminergic D2 receptors antag.
Nausea and vomiting regulation

- **mediators**

  - Chemoreceptoriney
    - Mediator: dopamin, serotonin

  - Cortex
    - Mediator: acetylcholin

  - Vomiting centre
    - Mediator: acetylcholin

  - Vestibullar apparatus
    - Mediator: histamin, acetylcholin

  - Larynx, stomach
    - Mediator: serotonin, histamin

Serotonin 5-HT3 receptor antag.
Nausea and vomiting regulation - *mediators*

Chemoreceptors
- mediator: dopamin, serotonin

Vomiting centre
- mediator: acetylcholin

Histamine H$_1$ rec. antagonists
- mediator: acetylcholin, histamin

Cortex
- mediator: acetylcholin

Vestibullar apparatus
- mediator: histamin, acetylcholin

Larynx, stomach
- mediator: serotonin, histamin
Nausea and vomiting regulation

- **Mediators**

  **Chemoreceptors**
  - Mediator: dopamin, serotonin

  **Vomiting centre**
  - Mediator: acetylcholin

  **Cortex**
  - Mediator: acetylcholin

  **Vestibular apparatus**
  - Mediator: histamin, acetylcholin

  **Anticholinergika**

  Larynx, stomach
  - Mediator: serotonin, histamin
**ANTIEMETICS**
– according mechanism of action

<table>
<thead>
<tr>
<th>Neurotransmitter</th>
<th>Antiemetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>serotonin</td>
<td>serotonin 5-HT$_3$ receptor antagonists <em>(setrons)</em> – (ondansetron, granisetron)</td>
</tr>
<tr>
<td>histamine</td>
<td>histamine H$_1$ receptor antagonists <em>(moxastin, diphenylhydramin)</em></td>
</tr>
<tr>
<td>dopamin</td>
<td>dopamin D$_2$ receptor antagonists</td>
</tr>
<tr>
<td></td>
<td>– type <em>neuroleptics</em> <em>(prochlorperazin, …)</em></td>
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<tr>
<td></td>
<td>– type <em>prokinetics</em> <em>(metoclopramid, …)</em></td>
</tr>
<tr>
<td>acetylcholin</td>
<td>anticholinergics <em>(skopolamin, atropin)</em></td>
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</tbody>
</table>
ANTIEMETICS – SETRONS
SEROTONIN 5-HT₃ rec. antagonists

• only one receptor subtype blockade.

• most effective antiemetics
  - blockade stimulation
    in periphery - GIT,
    in chemoreception center

• invaluable in onkology
serotonin and setrones

ondansetron – ZOFTRAN, granisetron – KYTRIL, tropisetron – NAVOBAN, …
ANTIEMETICS - SETRONS

ondansetron (Zofran)
- competitive inhibition

granisetron (Kytril)
- noncompetitive inhibition, longer duration (1 day)

palonosetron (Aloxi)
- noncompetitive inhibition, most effective and longest (5 days)
- AR: headaches, gut motility disturbances (constipation, cramps, diarrhea), fatigue, somnolence or insomnia,

indication: vomiting during chemotherapy
ANTIEMETICS
neurokinins antagonists

**aprepitant** (Emend)
- combined effect: substance P antag.+ inhib. 5-H3 rec.
- significant antiemetic effect, potenciation of setrons
- **indication:** vomiting during chemotherapy

"Royal combination,, for resistant vomiting
setron + dexamethason + aprepitant
(prochlorperazin)
ANTIEMETICS

H₁ receptors antagonists

- inhibition of vestibular stimulation
- indication: motion sickness (event. vertigo)
- AR: severe sleepiness (driving), dry mouth,

moxastin (Kinedryl), embramin (Medrin),
diphenhydramin

– preventive application
ANTIEMETICS

D₂ receptor antagonist

- mainly inhibited emetic stimulation from periphery GIT

- neuroleptics – sedation
  
  *thiethylperazin* (Torecan), *prochlorperazin*,

- prokinetics - increased motility of oesophagus and stomach
  
  *metoclopramid* (Cerucal): ↑ AR – HEB penetration extrapyramidal symptoms
  
  *domperidon* (Motilium) – does not penetrate to CNS, ↓ AR
ANTIEMETICS
complex effect

*Thiethylperazin* (Torecan)

- different receptors inhibition
  - dopamine D2
  - histamine H1
  - muscarinic

- significant antiemetic and anti-motion sickness
ANTIEMETICS

ANTICHOLINERGICS

- are not able to inhibit chemoreceptor stimulation
- muscarinic receptor inhibition.
- spasmyloytic effect
- supporting effect only, little importance

*scopolamine* (supporting treatment),
*atropine* - not regularly used
prokinetics
mechanism of action

- peripheral dopamine $D_2$ receptor inhibition
  - dopamine inhibits GIT motility

- acetylcholine agonists (myenteric plexus)
  - acetylcholin stimulate peristaltics
  - acetylcholinesterase inhibition
    - $\uparrow$ ACH availability in synapses
Prokinetics
–dopamine D$_2$ receptor inhibition

**metoclopramide** (Cerucal, Degan)

- antiemetic effect, cholinomimetic action, dopamine antag.
- gastro-oesophageal reflux, gastric emptying

- **lipophilic - passing HEB – central effects**
- **frequent AR 10-20%**
  - central - extrapyramidal (tremor), sleepenes
  - peripheral - diarrhoea
  - hyperprolactinemia – gallactorhea, menstruation abnormalities

➢ cheap, fast, and short time action – 1-2 hours
PROKINETICS

• **Domperidone** (Motilium)
  
  – selective dopamine $D_2$ receptor antagonists,
  
  – antiemetic effect
  
  – increasing GIT motility and smooth muscle tone,

AR – not passing HEB, less AR than metoclopramide

hyperprolactinemia present,

➢ longer effect 4-6 hours
PROKINETICS

- Cisapride – not on the market
  - stimulation of Ach release from myenteric plexus in upper GIT
  - increased gastric motility, increase sphincter tonus
  - long halve life 10 hours
  - no antiemetic action
  - diarrhoea, abdominal cramps, tachycardia
  - Q-T interval prolonged, dangerous interactions
  - erythromycin, ketokonazole, terfenadine
PROKINETICS – dual action

- **Itoprid** (Ganaton)
  - dual action: *peripheral D₂ receptor blockade*
  - ↑ Ach availability (acetylcholinesterase inhibition)
  - effect: ↑ tonus aesophageal sfincter (reflux)
    - ↑ gastric evacuation (for gastroparesis)
    - ↑ tonus and gut motility (paralytic ileus)
- AR – less common diarrhea, hypersalivation, hyperprolactinemia
  - more expensive, highly effective and well tolerated, quick onset - 30 min, duration 6-8 hod
Peptic ulcer

• proton pump inhibitors (PPIs)
  - Helicobacter pylori eradication

• enhancing mucosal resistance
  - $H_2$ antihistaminics
  - antacids
  - parasympatholytics
Peptic ulcer

• primary
  – gastritis with Helicobacter pylori infection

• secondary
  – produced by drugs (antireumatic, NSAISs, corticoids.now
  - stress, endocrinological abnormalities

(ZE syndrome),
Helicobacter pylori

• widest specific human infection
  (50 -70% patients in ČR infected)

• adaptation for acidic environment
  „alkalick cloud of ammonia“
  enzymatic splitting of uric acid to ammonia

• **detection:** urease test, breathing air antigen in the stool, histology during biopsy
The Nobel Prize in Physiology or Medicine 2005

"for their discovery of the bacterium Helicobacter pylori and its role in gastritis and peptic ulcer disease"

Barry J. Marshall, Australia

J. Robin Warren, Australia

« I preferred to believe my eyes, not the medical textbooks of the medical fraternity » R. Warren (2002)
Peptic ulcer treatment
Peptic ulcer treatment enhancing mucosal resistance

- prostanoids, bismuth salt
  - mucus
- prostanoids
  - bicarbonate
- prostanoids, sucralfat
  - mucosal protection
Neutralisation of gastric secretion
Reflux oesophagitis

- proton pump inhibitors
  - omeprazole, pantoprazole
- \( \text{H}_2 \) receptor antagonists
  - ranitidine, famotidine, antacids
    - aluminium, magnesium salt
- bismuth chelates
HCl secretion schema

HCl

H^+  K^+  Cl^-  HCl

muscarinic r.  H2 rec.  gastrin r.

Ach  histamin  gastrin

mast cell.

n.vagus  food
HCl secretion schema

HCl secretion involves the movement of ions across the parietal cell membrane:
- Proton pump inhibition
- Muscarinic receptors
- H2 receptors
- Gastrin receptors
- Ach (acetylcholine)
- Histamin
- Gastrin
- Mast cell

Food triggers gastrin release, which stimulates proton pump activity, leading to HCl secretion.
HCl secretion schema

HCl

H+  K+  Cl-

muscarinic r.  H2 rec.  gastrin r.

Ach  histamin  gastrin

mast cell.

n.vagus  anticholinergics  atropin

lumen  parietal. cell

food
HCl secretion schema

HCl

H⁺  K⁺  Cl⁻

muscarinic r.  H2 rec.  gastrin r.

Ach  histamin  gastrin

n.vagus  mast cell.

H2 rec. antagonists

lumen  parietal. cell

food
HCl secretion schema

HCl

H⁺  K⁺  Cl⁻

muscarinic r.  H₂ rec.  gastrin r.
Ach  histamin  gastrin

mast cell

n.vagus

PGE
misoprostol

lumen
parietal. cell

food
HCl secretion schema

antacids $\rightarrow$ HCl

$\text{H}^+$, $\text{K}^+$, $\text{Cl}^-$

muscarinic r.  H2 rec.  gastrin r.

Ach  histamin  gastrin

mast cell.

n.vagus

parietal. cell

lumen

food
Proton pump inhibitors - PPI

- the most effective inhibition of gastric HCl secretion
PROTON-PUMP INHIBITORS

- Omeprazole, pantoprazole, lanzoprazole, rabeprazole
- Irreversible inhibition of H⁺/K⁺-ATPase
  - proton pump, terminal step of acid secretion
- inhibition of basal and stimulated secretion
- half life relatively short, but single dose effect last 2-3 days
- side effects - not common, headache, diarrhoea, rashes, dizziness, somnolence, mental confusion, impotence, pain in muscles and joints
- most effective, Helicobacter pylori eradication, NSAID ulcer
Omeprazol – metabolic interactions

- metabolised by CYP2C19 oxidase (+CYP3A4)
- omeprazol inhibits CYP2C19 oxidase – affects a series of drugs metabolism and effects
- slows down metabolism of diazepam
Clopidogrel bioactivation

85% inactive metabolites (esterase)

hydrolysis (esterase)

clopidogrel - pro-drug

oxidation (CYP3A4, 2C19, ...)

15% active metabolite (oxidase)
Pantoprazol

Same mechanism of action as omeprazol

- slower onset of action 1-3 h.,
- longer duration of action
  - secretion restored after 1 week
- weaker inhibition CYP2C19 than omeprazol
$H_2$ receptor antagonists

- fully replaceable by PPI
H$_2$ antagonists

- Competitive inhibition histamine stimulating secretion,
  - H$_2$ receptors blocking
- Ranitidine, Cimetidine, Famotidine, Nizatidine,
- OTC
- Side effects
  - cimetidine – only for short term treatment
  - hepatic enzyme inhibition
  - potentiates oral anticoagulants, fenytoin, carbamazepine, quinidine,
  - antiandrogenic effect
Antacids

today only symptomatic,
fast acting treatment of pyrosis
(heartburn)
Neutralisation of gastric secretion
Reflux oesophagitis

• **ANTACIDS**
  - great number of products
  - Magnesium and Aluminium salt
  - galenic form important
  - frequent dosage
  - long lasting treatment
Neutralisation of gastric secretion

**ANTACIDS**

- **Magnesium hydroxide**
  - insoluble powder, no systemic alkalosis
- **Magnesium trisilicate**
  - insoluble, long lasting effect
- **Aluminium hydroxide gel**
  - strong action, several hours,
- **Sodium bicarbonate**
  - rapid action, carbon dioxide, rebound phenomenon, absorption, can cause alkalosis, do not use
- **Alginate**
Neutralisation of gastric secretion
ANTACIDS

• **Interactions**
  – TTC, fluoroquinolons, penicilamine, fluorides, bisfosfonates
  – azithromycine, nitrofurantoin, rifampycine, fenytoine, chlorochine, antipsychotics, domperidone
  – Li + bicarbonates

• **enterosolvent tablets**
Drugs which protect the mucosa

- supporting therapy of peptic ulcer
- drugs of the second to the third choice
Drugs which protect the mucosa

- **Bismuth chelate**
  - coloidal bismuth subcitrate, subnitrate, ranitidine bismuth citrate

- **Sucralfate**
  - aluminium hydroxide - sulphated sucrose
  - complex gel, high binding power, not absorbed

- **Misoprostol**
  - prostaglandine derivative - PGE$_1$, inhibits gastric secretion, mucosal protection,
  - NSAIDs ulcer protection
Helicobacter eradication

proton pump inhibitors
antibiotics + chemotherapeutics
bismuth salt
Helicobacter eradication and ulcus recurrence

no eradication     eradication

recurrence (%) per year
Helicobacter eradication strategy: triple therapy

- combination two ATB + IPP
  (or ATB + chemotherapeutics + IPP)

- ATB: amoxicillin, klaritromycin, tetracycline, azithromycine, or chemotherap. metronidazol,

- PPI: omeprazol, pantoprazol

- eradication usually within one week,
The most frequently used combinations for eradication

- Omeprazol 40 mg (or pantoprazol 80 mg) daily
  + Amoxicillin 2x 1 000 mg
  + Metronidazol 2x 400 mg

- Omeprazol 40 mg (or pantoprazol 80 mg) daily
  + Metronidazol 2x 400 mg
  + Clarithromycin 2x 250 mg

- Omeprazol 40 mg (or pantoprazol 80 mg) daily
  + Amoxicillin 2x 1 000 mg
  + Clarithromycin 2x 500 mg
Spasmolytics

- symptomatic treatment of acute and chronic diseases accompanied by GIT smooth muscle hypertony
- heterogeneous group of drugs,
- common mechanism of action relaxing effect on the smooth muscle
Spasmolytics

• **neurotropic spasmolytics** - parasympatolytics

• **musculotrophic spasmolytics**
  papaverine like
  calcium channel blockers

• **nonspecific spasmolytics**
  (nitrates, local anesthetics)
neurotropic spasmylytics

- derivatives of Atropa belladona alkaloids
- spasmylytic effect during hypertrophy, hyperkinesia or dyskinesia of smooth muscle
- release of stomach, gut, gall bladder and urinary tract spasm
Parasympatolytics

a) non-selective (general muscarinic receptor blockade – also bronchial, urogenital)
   – atropin
   – scopolamine
• butylscopolamine (Buscopan)
   – otilonium
   – ipratropium (also antiasthmatic)

b) selective - specific muskarinic M₁ rec. blockade
   – pirenzepin (not in ČR)
musculotropic spasmsolics

a) papaverine-like type

- direct smooth muscle relaxation - increased cAMP (phosphodiesterase inhibition)

- papaverine – opium alkaloid without analgetic effect and euphoria, also vazodilatation

- usually in combinations

- pitofenon (in combinations Algifen)

- drotaverin (Nospa) strong spasmsolytic

- indication: irritable bowel, billiary colic
musculotrophic spasmodylitics

b) calcium channel blockers

• *pinaverin* (Dicetel)
  – selective inhibition calcium channel

• **indication:** irritable bowel, biliary colic
Adverse reactions of spasmolytics

• **parasympatolytics**
  - tachycardia, tachyarytmia
  - urine retention
  - excitation
  - increased intraocular pressure
    (cave: glaucoma)
  - accommodation disorders - midriásis

All others **spasmolytics and opioids**

- paralytic ileus
- toxic megacolon
LAXATIVES
The balance of intake and secretion with absorption of fluids in GIT
Secondary causes of obstipation – drug induced

- anticholinergics
- antacids
- antihistaminics
- CCB
- diuretics
- opiates
- psychotropics
- NSA
- sympatomimetics
- ferrum
Laxatives

• contact
  – senna, bisacodyl, fenolftalein, pikosulphate

• osmotic
  – laktulose, magnesium hydroxide and sulphate, glycerin

• bulking agents
  – methylcelulose, agar, Plantaginis ovatae testa ispaghula husk

• softening
  – paraffin oil
STIMULANT LAXATIVES

**mechanism of action:** increase peristalsis

- primary stimulation nervous plexus (colon)
- Na pump inhibition - more electrolytes in the lumen sekundary peristaltic stimulation

- onset of effect: 4 - 12 h, suppository 10 min.
- **AR:** intestinal spasm, gut paralysis
  - mucosal damage
  - not use chronically
**STIMULANT LAXATIVES**

**bisacodyl** (low toxicity)
- tbl – evening application – morning effect
- supp – morning application – effect during 15min. up to 1hour

**phenolphthalein**
- effect in colon – after 10 - 14 hours
- enterohepatic circulation – effect for days
- rash
STIMULANT LAXATIVES

antrachinons
– antracene derivatives (glykosides)
– effect only in colon, where hydrolysed
– myenteric plexus stimulants + sodium active transport block ⇒ dual peristaltic stimulation
  • onset after 6-12 hours
  • do not use during pregnancy, excretion to milk!!!

senna – plant, natural product
• glykosides (sennosides similar to antrachinons)
• only for short term use
OSMOTIC LAXATIVES

**lactulose** (non irritant, mild)
- disacharid no resorbable
- splitting in colon to $\downarrow$ resorbable fructose and galactose $\Rightarrow$ osmotic flow to the lumen
- effect after 12-24 hours

**glycerol**
- suppository – effect after 15 - 30 min

**hydroxyd and magnesium sulphate**
- $\downarrow$ solubility, non-resorbable, osmotic activity
ANTIDIARRHOEAL DRUGS
Causes of acute diarrhoea (<14 days)

- infections
- drugs
- ischemic colitis
- mesenteric artery thrombosis
- acute diverticulitis
Causes of chronic diarrhoea (>14 days)

- inflammation – nonspecific and radiation colitis
- osmotic – absorption disturbances - pankreatic insufficiency
- secretion – karcinoid, ZE syndrome
- motility disturbances – irritable bowel, neurological diseses.
- arteficial – laxative overuse
ANTIDIARRHOEAL DRUGS

• diarhoe is only symptom
  – „travellers diarrhoea“
  – necessary to treat the cause

mechanism of treatment:
• decreased toxins absorption (adsorption)
• decreased motility – prolong time for reabsorption of electrolytes - (opioids)
• elimination of infection (desinfectants, ATB)
• changed gut microflora - (probiotika)
ANTIDIARRHEAL DRUGS - adsorbentia

- non-resorbable, activated surface
- mainly for infections as supporting therapy

- *Carbo adsorbens*, kaolin
- *potassium magnesium aluminium silicate* (*diosmektit*)
ANTIDIARRHOEAL DRUGS

decreased motility

direct stimulation of opioid receptors \( \mu \)

- slowdown propulsion and secretion in the gut

- \textit{loperamid} (Imodium) – opioid,
  – non resorbable

- \textit{tinctura opii}
ANTIDIARRHOEAL DRUGS - chemotherapeutics

- **chloroxin** (Endiaron)
  - chinolone type chemotherapeutic
  - effect on G- and G+
  - after long time treatment (>4 weeks)
  - neurotoxicity

- **nifuroxazid** (Ercefuryl)
  - wider spectrum than chloroxin

- fluorochinolons – *ciprofloxacin, ofloxacin, norfloxacin*
ANTIDIARRHOEAL DRUGS

antibiotics

• **rifaximin** (Normix)
  - bacteriostatic and bactericidal ATB
    - G+ and G- spectrum
  - non resorbable
  - risk of resistance relatively high and quick
„travellers diarrhoea“

Non specific treatment

• rehydratation, diet
• adsorbentia - *carbo adsorbens, diosmectit* (Smecta)
• chemotherapeutics – *chloroxin* (Endiaron),
• decreased motility – *loperamid* (Imodium) –
  contraindication – blood in stool or fever
• probiotics
„travellers diarrhoea“

- ATB only for severe course (fever)
- *chloroxin* (Endiaron), *nifuroxazid* (Ercefuryl)

- (fluorochinolons) - *ciprofloxacin*, *norfloxacin*, *ofloxacin*
  - *Only last choice – development of resistance*

- *rifaximin* (Normix)
probiotics (eubiotics)

- freeze-dried culture – viable, non-patogenic strains E.coli or Saccharomyces
  • modulation of the intestinal microflora, restore physiological gut flora

indications: supporting care
  • Irritable bowel, chronic diarrhoea, meteorism ,
  • constipation
  • Nonspecific inflammation (Crohn disease), snížení dysmicrobia after ATB treatment