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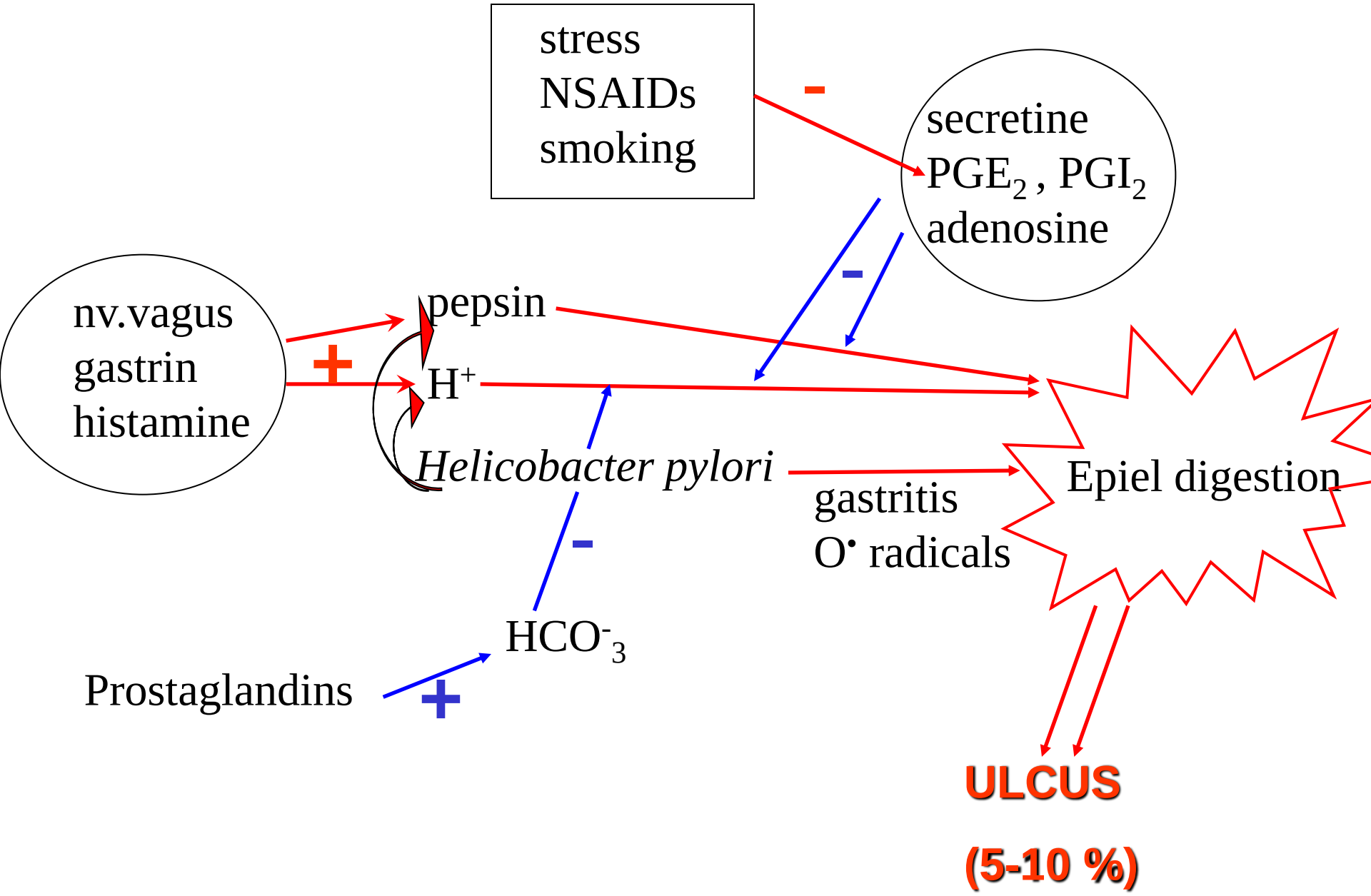
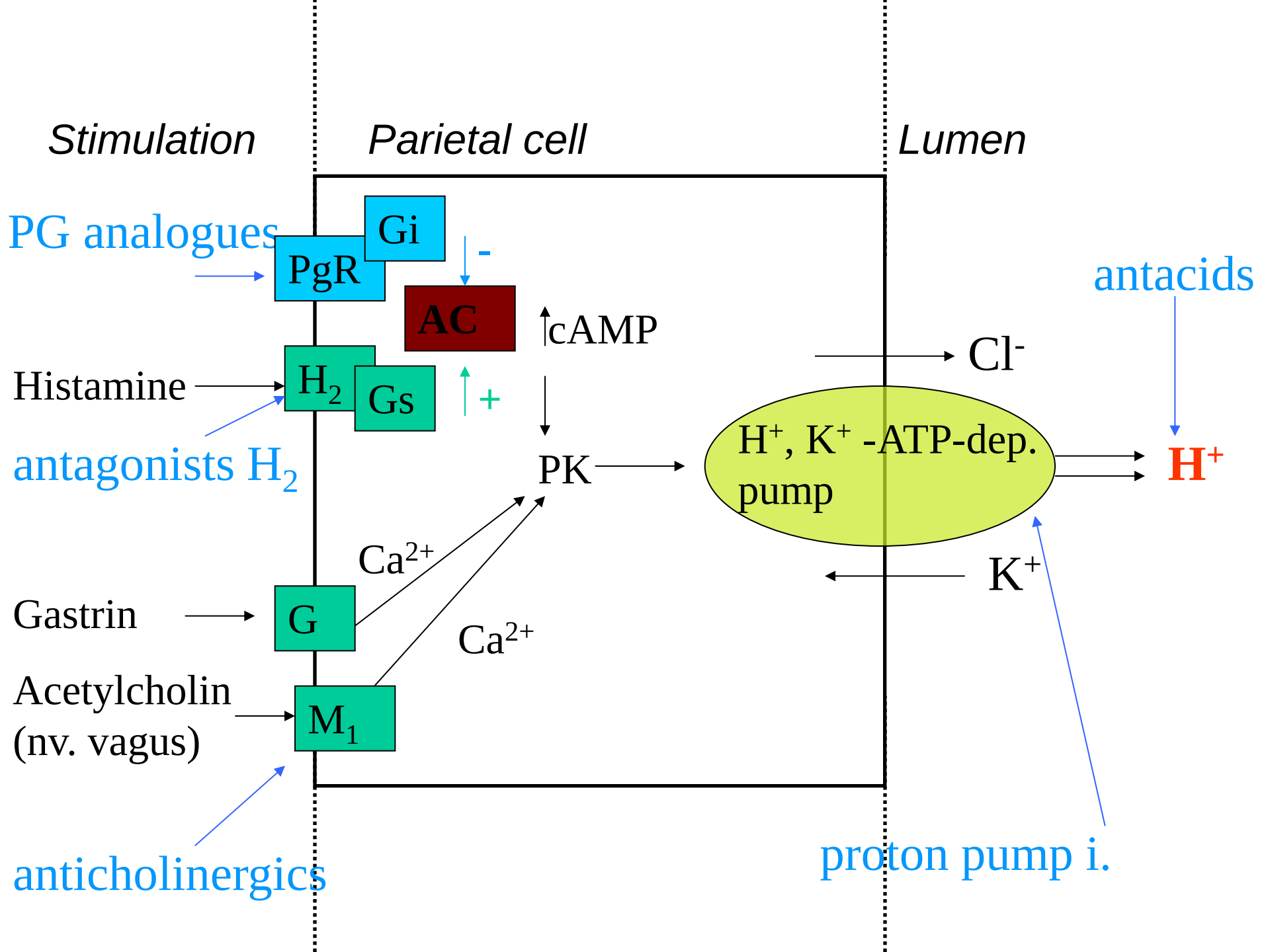
Dpt. of Pharmacology

Drugs used in gastric ulcer disease

Peptic ulcers – result of dysbalance between protective and harmful factors

Protective factors	Harmful factors
mucin, mucus	H^+
HCO^-_3	pepsin
epitelium, mucous barrier	*Helicobacter pylori*
perfusion in gastric mucosa	NSAIDs
	corticosteroids


stress
NSAIDs
smoking
-
secretine
PGE2 , PGI2
adenosine
-
nv.vagus
gastrin
histamine
+
pepsin
H+
Helicobacter pylori
-
HCO-3
Prostaglandins
+
gastritis
O• radicals
Epiel digestion
ULCUS
(5-10 %)


Stimulation
Parietal cell
Lumen
PG analogues
PgR
Gi
-
AC
cAMP
antacids
Histamine
H2
Gs
+
Cl-
antagonists H2
PK
H+, K+ -ATP-dep. pump
H+
Ca2+
Gastrin
G
Ca2+
K+
Acetylcholin
(nv. vagus)
M1
anticholinergics
proton pump i.

AIMS of TREATMENT

- supress pain
- improve healing (mucosa reparation)
- prevent relaps

neutralization (antacids)

supress harmfull factors

(HCl, pepsin, H. pylori)

mucosa resistence increase

Drugs used in ulcer disease

- Antacids
- Inhibition of HCl secr. - H_2 antagonists
  - H^+ pump antagonists
  - anticholinergic drugs
- Eradication of *H. pylori*
- Cytoprotective drugs

Antacids

- symptomatic therapy
- HCl neutralisation in stomach = increase in pH...decr. pepsin activity (pH optimum 2)

Antacids

- $NaHCO_3$ (strong, rapid relief from pain)
- $CaCO_3$ (strong, rapid relief from pain, not for chronic treatment absorption of Ca^{2+})
- MgO / $Mg(OH)_2$ (laxative)
- $Mg\ [AlO_2(OH)]$

  $Mg(OH)_2 + Al_2O_3$
- Al_2O_3 (gel, long-lasting, constipation)
- $Bi(OH)_2NO_3$ (wek eff., supress *H. pylori*)

Antacids

Indications:

dyspepsia, hyperacidity, pyrosis, reflux oesophaagitis

symptomatic treatment of GIT disorders

begining of antiulcerous therapy, rapid relief from pain

ADE: absorption of Ca, Mg (cardiac complications)

- Al – constipation, Mg - laxative
- decr. absorption of other drugs

Inhibition of HCl secretion

1) H_2 antihistaminics

2) Proton pump inhibitors

3) Anticholinergics

H_2 antihistaminics

Mechanism of action:

competitive H_2 receptor antagonisms

selective supression of HIS-induced secretion

inhibition of intrinsic factor secretion (B_{12})

H_2 antihistaminics

~~cimetidine (Cimetidin, Primamet)~~-withdrawn

ranitidine (Apo- ranitidine, Ranisan, Ulcosan, Ranitan, Zantac, Histac)

famotidine (Apo-Famotidin, Famosan, Quamatel, Ulfamid)

nizatidine

roxatidine

H_2 antihistaminics

Indications: ulcer disease

secondary ulcer disease

prevention of peptic ulcer relapse

Zollinger-Ellison syndrome (↑gastrin)

reflux oesophafgitis

hyperacidity, NSAIDs treatment

H_2 antihistaminics

ADR: headache, myalgia, diarrhoea, constiption,

CNS - confusedness, glossolalia

endocrine - antiandrogenic efect (cimetidine)

- impotence, gynekomastia

blood – granulocytopenia, trombocytopenia, neutropenia..aplastic anemia

(cimetidine, ranitidine)

hepatotoxicity – ALT, AST

Caution: passes placental barrier,

Proton pump inhibitors

- very strong effect
- supress HCl secretion not concerning the origin of stimuli
- enterosolvent coating, parenteral
- administered as a pro-drugs

Proton pump inhibitors

Mechanism of action

- H^+ conditions$\rightarrow$active metabolites
- irreversible inhibition
- Re-synthesis needed for regeneration

Proton pump inhibitors

- omeprazole (Helicid, Apo-Ome, Gasec)
- pantoprazole (Controloc, Pantoprazol)
- lansoprazole (Lansul)
- rabeprazole

Proton pump antagonists

Indications

- constituent of *H. pylori* eradication in ulcer disease
- ulcer disease in H_2 antagonists failure
- reflux oesophagitis
- Zollinger-Ellison syndrome (↑gastrin)

Proton pump antagonists

ADR

- dyspepsia, headache
- rarely cytopenia
- P450 inhibition

Selective parasympatolytics

Mechanism of action: acetylcholine antagonism in M_1 receptors

- convenient is ***selective*** inhibition
- supress CO^{2-}_3 and mucus secretion
- Similar action with H_2 antagonists

Selective parasympatolytics

pirenzepine

Indications: peptic ulcer disease

dyspepsia after NSAIDs treatment

stress ulcer prevention

CI: glaucoma, prostate hypertrophy, micturition disorders

Cytoprotectives

Mucus- protective eff. on the na mucosa of stomach

Sucralfate

Bismuth salts

Alginic acid

Cytoprotectives

Sucralfate – octasulfate of sucrose + aluminium hydroxide

(Sucrolan, Venter,Ulcogant)

Effects

strong mucoprotective eff.

protective barrier set up

Binds pepsin and bile acids

Incr. prostaglandins synthesis

Sucralfate – octasulfate of sucrose + aluminium hydroxide

ADR

not absorbed → mild ADR

dyspepsia, Al- constipation

Rarely plasmatic Al elevation

Decr. bioavailability of other drugs - TC, phenytoin,digoxine, cimetidine...

Bismuth salts – basic salts of bismuth and citric acid

Mechanism of action

Chelatation of proteins on ulcer surface $\rightarrow$ protective barrier

PG secretion stimulation

antibacterial action (eradication of *H. pylori*)

Alginic acid

Proves protective barrier-gel on the surface of stomach mucous

Effect lasts app. 2.5 h

Eicosanoids

$PGE_{1,}$ PGI_2 – main natural protective factors

synthetised in gastric mucosa

Incr. mucus and HCO_3 production, perfusion

Unstable, only derrivatives administered as prevention of harmfull effects of NSAIDs

Cytoprotective and antisecretive drugs

Rioprostil, enprostil, misoprostol

Misoprostol

- methylester PGE_1
- long-lasting effect
- abortive !
- ADE- dysepsia, nausea, flatulence

Eradication of *H. pylori*

(G- bacteria)

decrease frequency of relapses to 0-10 %

complex therapy – together with H+ pump inhibitors

Combination of 2 antibiotics

metronidazole + amoxycilin

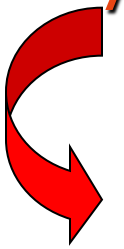
metronidazole + claritromycin

metronidazole + tetracyclin

Antiemetics, prokinetics

Initiation of vomitting

A) Chemoperception area (area postrema)



apomorphine, digitalis, nicotine, $CuSO_4$,toxins, uremia

B) Formatio reticulraris – (CNS center of vomitting)

sympathetic and parasympathetic inervation

kinetosis

incr. Intracranial pressure

pregnancy

psychogenic factors

inflammation, peritoneal distension

delayed gastric emptying

Initiation of vomitting

B) formatio reticularis

C) Efferent nerves VIII-X – pylorus sfincter contraction

- cardia opening
- abdominal muscles contraction
- reflux peristaltic moevements in oesophagus

Influence of neurotransitters on vomitting

- dopamine - D_2 receptors
- histamine - H_1 receptors
- serotonin - $5HT_3$ receptors
- acetylcholine - M receptors
- enkephalins (+opioids) - δ, κ- receptors
- GABA

Antiemetic drugs

- anticholinergic drugs
- antihistaminics (H1)
- neuroleptics
- $5HT_3$ antagonists
- cannabinoids
- neurokinine antagonist
- prokinetic drugs (incr. motility)
- Ca^{++} channel blockers
- ginger extracts (*zingiber off*.)

Anticholinergic drugs

Scopolamin (TTS)

- acts centrally + peripherally
- for kinetosis in the dose 0.5 mg
- ADE: sedation, constipation, urine retention and others anticholinergic ADE

Antihistaminics

- H1 antihistaminics of the 1.st generation – anticholinergic action, pass through BBB

- sedative action

  → convenient use in kinetosis

- insufficient action in severe vomitting after chemotherapeutics (oncology)

Antihistaminics

Drugs used in practice

difephehydramin theoclate = dimenhydrinate

(Travel-Gum, +cinnarizin = Arlevert, +Paracetamol = Migraeflux)

moxastine theoclate = mefenhydrinate

(Kinedryl)

embramine theoclate = mebrofenhydrinate

(Medrin)

promethazine (Prothazin)

Antihistaminics

theoclates (salts of H1 antagonist + 8-chlortheophylline)

- weak sedation, low occurence of ADE
- augmented antivertiginous effect
- prolonged $T_{1/2}$

ADR: ADE: sedation, fotosensitivity, allergy, dry mouth, urine retention etc..

Caution: prevent combination with other sedative drugs (opioids, hypnosedatives, neuroleptikcs)

pass BB, placenta

Neuroleptics

- inhibit vomitting center in f. reticularis
- strong antiemetic effect
- except of thietylperazine ineffective in kinetosis
- lower doses than in psychosis
- sufficient effect in nausea ad vomitting after antineoplastic treatment
  X weaker effe. Compared to procinetics + i 5HT3 receptors (setrones)

Neuroleptics

Phenothiazines

prochlorperazine

perphenazine

thiethylperazine (Torecan inj., drg., supp.)

ADE: sedation, tiredness, dry mouth, constipation, fotosensitivity, extrapyramidal symptoms.

Thiethylperazine can be administered in 1st. trimester of pregnancy

Neuroleptics

Butyrophenons

haloperidol

droperidol – prior to general anaesthesia, severe vomitting in cytostatic treatment

ADE: haloperidol- somnolence, tiredness, hypoglycemia, constipation

droperidol- rare – neuroleptic syndrom (10% mortality)

$5HT_3$ receptor antagonists

- in the peripheral tissues - block n. vagus stimulation
- in the vomitting center (f. reticularis)
- absence of sedative eff.
- more eff. in cytostatic treatment than prokinetics and glucocorticoids

ADE: constipation, headaches, vertigo, ↑ALT,AST

$5HT_3$ receptor antagonists

Palonosetron (Aloxi)

ondansetron (Emeset, Emetron)

granisetron (Kytril)

dolasetron (Ansemet)

tropisetron

Neurokinin receptor antagonist

NK-1 receptors in brain stem, area postrema, n. tractus solitarii in medula oblong.

NK_1-rcp vagal endings in oesophagal sfincter

NK_1- agonist is substance P, and neurokinine neuropeptide, 11 AMK)

Aprepitant – antag. NK_1 rcp., binds substance P

NK1 rcp antag. = anxiolytic, antidepressant actions, supresses proliferation

Prokinetics

Peristalsis stimulation GIT (proximal part)

partial antagonists of D_2 and 5HT receptors

Indications: nausea, vomitting, reflux. oesophagitis, prevention of bile reflux, improvement of gastric emptying

Prokinetics

Metoclopramide (Cerucal, Degan, Pramidin)

Cisapride (Prepulsid)

Domperidone (Motilium)

Alizapride

(levo)Sulpiride – antipsychotic drug, antiemetikum

(Prosulpin, Sulpirol, Dogmatil)

→ psychoaffective disorders with somatic symptoms

Cannabinoids

Dronabinol -

Nabilon -

Not in clin. practice, unknown mechanism of action, acting centrally + peripherally

Antivertiginous Ca^{++} channel blockers

cinnarizine
flunarizine
} vasodilation, antivertiginous eff.
structurally related to anti-H_1

Indications : vertigo due to impaired cerebral perfusion

Stugeron, Cinnabene, Arlevert (+ dimenhydrinate)

Antiemetics

Corticosteroids - nonspecific – membrane stabilizing effects

- decrease of sy.PG

→ combined with metoclopramide in nausea after cytostatic treatment

Dexamethasone, Methylprednisolone

Ginger - *Zingiber officinale* - zingiberol and gingerol

→ mild nausea symptoms in pregnancy

→ peripheral action

Indications of antiemetic drugs

PREGNANCY: thietylperazin (Torecan supp, inj. drg.)
vit. B6 (pyridoxine)
ginger

POSTOPERATIVE : domperidone
metoclopramide

KINETOSIS, VERTIGO antihistaminics (anti H_1, H_3)
- phenothiazines (anti H1 and PSL)
- parasympatolytics
- Ca blockers

AFTER CYTOSTATICS, IRRADIATION: 5-HT_3 rcp antagonists, combination metoclopramide + corticosteroids

Emetics

Indication: weaning alcohol addicts,treatment of overdose (consciousness)

Apomorphine - stimulation of D_2 rec. in area postrema (in medulla oblongata)

- 5-10 mg s.c. $\rightarrow$ intense vomitting

ADE: vertigo, sedation, hypotension, euphoria, coma

Emetics

Emetin

Cephaelis Ipecacuanha – radix (roots)

10-15 mg $\rightarrow$ vomitting

1-2 mg $\rightarrow$ expectorative eff.

Disulfiram

Inh. aldehyddehydrogenase $\Rightarrow$ acetate, ketones
$\Rightarrow$ vomitting center stimulation

Alcohol + Cephalosporins, Metronidazol, Sulphonylureas