BIOP211 – Pharmacology

Tutorial Session 8 Drugs Affecting the Blood, Lipid-lowering Drugs and Drugs Affecting the Gastro-intestinal Tract, GIT

- Students practise the use of MIMS online and other Online Drug / Herb monographs for activities on Drugs Affecting the Blood, Gastro-intestinal Tract, GIT and Lipid-lowering drugs
- Drug-herb interactions research – Case study Herbs and Drugs used in peptic ulcer disease PUD
- Handout on PUD and GORD is included below in your Tutorial Handout

8.1.1 Discus the following drugs/ drug classes

- Lipid lowering drugs: hydroxymethylglutarylCoA reductase inhibitors (Statins)
- Lipid lowering drugs: fibrates, bile acid binding resins and Niacin
- Warfarin and its antidote (antagonist in overdose)
- Proton pump inhibitors
- H2 antagonists
- Cytoprotective agents and antacids

Your answer should cover the following

- Examples and indications.
- Mechanism of action.
- Efficacy and limitations or cautions / contra-indications.
- Adverse effects and drug interactions with nutrients and herbs.
- For warfarin use the LibGuides eBook by Veitch, Barnes, Smith, Phillipson and Anderson (2014) to find other coumarins.

Use peer review to mark your responses out of 10 marks each.

8.1.2 To assist you with your revision of Pharmacodynamics and Pharmacokinetics for the final assessment, answer these questions. Feedback is available through the Review Quizzes 8 and 13 (Endeavour LMS).

- Use Online resources or the Appendix in your text (Herb-, Nutrient- and Food-Drug Interactions) to list four (4) absorptive (or other pharmacokinetic) drug interactions that are drug-herb or drug-nutrient interactions.
- Use online resources or the Appendix in your text (Herb-, Nutrient- and Food-Drug Interactions) to list some pharmacodynamics drug interactions that are drug-herb or drug-nutrient interactions.
From subject website, review diseases Peptic Ulcer Disease, PUD, GORD, in Handout on PUD & GORD, Practice using Drug Monographs and Herbal Medicines Monographs from Medicines Complete™ (LibGuides link on Endeavour Library Website). Then reflect on the case study and answer the Quiz on Mr U below. Answers are available in Endeavour LMS Session 8 Review Quiz.

Mr U, a 45 year old man, is currently not on anti-hypertensive therapy. Mr U is about to start triple therapy with antibiotics and a proton pump inhibitor. This is to eradicate Helicobacter pylori following a positive 13C urea breath test and endoscopy, which revealed two duodenal ulcers. He asks you as his complementary health practitioner if he can use ginger to relieve pain in his gut area. What would you recommend for Mr U? Check on Martindale (Brayfield, 2014) or Herbal section of Medicines Complete™ (Veitch et al, 2014) (see LibGuides link on the Endeavour Library site). Alternatively, see http://evolve.elsevier.com/AU/Bryant/pharmacology Complementary and Alternative Medicine content with crossword puzzles and choose <Case Studies>

As Mr U’s complementary health practitioner, you warn him that ginger improves gastro-intestinal motility but that ginger also

a) lowers blood pressure and so would aggravate Mr U’s hypertension
b) stimulates gastric acid secretion which would aggravate Mr U’s duodenal pain
c) stimulates the growth of normal flora organisms in the bowel
d) inhibits metabolizing enzymes for his antibiotic

As his complementary health practitioner, you recommend that Mr U try probiotics to

a) decrease the adverse effects of antibiotic therapy
b) counteract the antibiotic induced diarrhoea
c) stimulate the growth of normal flora organisms in the bowel
d) all of the above

What mucoprotective herbs could be recommended for Mr U?

a) ginger and acetyl salicylic acid (ASA) from willow bark
b) marshmallow and liquorice
c) peppermint oil
d) there are no mucoprotective herbal remedies

Of the herbal remedies given in the previous question, ginger, ASA (a salicylate) from willow bark, marshmallow, liquorice, which one is also anti-inflammatory and antibacterial, making it a valuable herbal medicine for peptic ulcer disease?

a) Ginger
b) Acetylsalicylic acid, ASA, from willow bark
c) Marshmallow
d) Liquorice

What further advice or management strategies would you suggest for Mr U?

a) Check his blood pressure and if needed, encourage him to see a general practitioner regarding anti-hypertensive medication
b) Check for herb-drug interactions once the anti-hypertensive medication is known to you
c) Get Mr U to inform his general practitioner about herbal medicines that he is currently taking
d) All of the above

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8.3 Review Quiz. Use your textbook. Feedback is available in Review Quiz 8 (Endeavour LMS)

Anti-coagulant and Antiplatelet drugs – Review (true / false). Use your textbook and lecture notes.

Feedback on the subject website:

1. Ciprofloxacin, metronidazole and erythromycin are all antibiotics that increase the anticoagulant effect (increased INR) of warfarin.

2. International normalised ratio (INR) measures the overall activity of the extrinsic coagulation pathway.

3. An antidote for excess warfarin therapy is vitamin K.

   Antidote is an antagonist drug given when a substance has been taken in excess.

Answers for the following are given for discussion:

4. Ticlopidine is an antiplatelet agent.

   True

5. A patient on warfarin therapy should be monitored by use of the activated partial thromboplastin time (APTT).

   False, the international normalized ratio (INR) is used to monitor warfarin therapy.

6. It is important to keep iron tablets well away from children because iron has almost no mechanism for excretion from the body and overdoses may be fatal

   True, review the physiology

7. The intake of green, leafy vegetables can result in decreased anticoagulant effectiveness of warfarin:

   True, green leafy vegetables are a source of an important vitamin which antagonizes the effects of warfarin.

8. Fibrinolytic drugs (e.g. alteplase, reteplase and tenecteplase) dissolve clots by activation of plasminogen to plasmin and this digests or dissolves fibrin clots.

   True, review the physiology

9. Dipyridamole is an anti-coagulant.

   False, agents which target platelets are more correctly called anti-platelet agents.

10. Sodium bicarbonate NaHCO₃ should be avoided in people with heart failure or hypertension because it increases the likelihood of fluid retention.

    True, review the physiology of Na⁺, because it is important for you to be able to synthesize your knowledge about Drugs Used to Treat Cardiovascular Disorders (Session 13) and Drugs used to Treat Gastro-intestinal disorders (Session 8) and their mechanisms of drug-drug interaction.
8.4 Handout Peptic Ulcer Disease PUD and Gastro-oesophageal Disease GORD

Peptic Ulcer Disease, PUD

The goals of peptic ulcer disease treatment are to:

- Relieve ulcer pain
- Encourage ulcer healing
- Prevent ulcer recurrence
- Avoid ulcer-related complications

The treatment of PUD focuses mainly on short-term drug therapy of ulcers and eradication of *H. pylori* infection.

Non-pharmacological management PUD:

Avoidance of unnecessary NSAID and aspirin use

- One of the main causes of PUD

Address underlying social / lifestyle factors that may exacerbate ulcer e.g. stress

- Note that the role of stress in PUD is considered controversial. Psychological factors appear more significant in some patients than others
- As a group – ulcer patients have been characterized as having a tendency to repress emotions

Cessation of smoking

- Impairs the healing rate of ulcers
- Decreases pancreatic bicarbonate secretion (gastric acid neutralizer)
- Increase in reflux of bile salts into the stomach
- Acceleration of gastric emptying time into the duodenum

- **Avoid** foods that may exacerbate symptoms
  - E.g. coffee, carbonated drinks, alcohol, spices, chillies, sugar, allergenic foods

- **Increase intake** of foods that may promote healing
  - Cabbage (glutamine)
    - Raw cabbage juice is well documented as an effective treatment in PUD
    - 1 litre fresh juice/day in divided doses has resulted in total ulcer healing in 10 days on average
  - Fibre (especially duodenal ulcers)
    - Plant based dietary fibre appears to offer better results than supplemental fibres (pectin, guar gum, psyllium) (Pizzorno et al, 2006)

PUD – elimination of *Helicobacter pylori* as an opportunistic pathogen in the stomach mucosa:

- Helicobacter pylori (*H. pylori*) is a gram negative bacteria that is well adapted to living below the layer of gastric mucosa.
- It is generally considered to be part of the “normal” or indigenous flora that most humans acquire in childhood and carry for life in their stomachs.
- Most patients carry *H. pylori* without developing any symptoms but occasionally, however, a small number of *H. pylori* carriers (15-20%) go on to develop peptic ulcer disease.
- **Virtually all patients with PUD (where NSAID use has been excluded) have evidence of *H. pylori* infection.**
- *H. pylori* has also been associated with an increase in gastric cancer (it has been classified as a class I carcinogen by the WHO) although a causal relationship has not yet been established.
The evidence for the important role of *H. pylori* in PUD is indicated in the facts that:

- Over 90% of patients with duodenal ulcer and more than 70% of patients with gastric ulcer are infected with *H. pylori*.

- The recurrence of duodenal and gastric ulcers is dramatically reduced following the eradication of *H. pylori* infection.

- There are various treatment protocols available for *H. pylori* eradication, most of which include 2 antibiotics and a proton-pump-inhibitor ("triple therapy").

- Intense drug treatment is usually prescribed for a period of 7 days.

- Susceptibility of *H. pylori* to antibiotics major factor in success of therapy (antibiotic resistance does occur – therefore, patient education to maintain correct regimen for the whole treatment period, avoids natural selection of resistant strains).

- Over 90% of patients with duodenal ulcer and more than 70% of patients with gastric ulcer are infected with *H. pylori*.

- The recurrence of duodenal and gastric ulcers is dramatically reduced following the eradication of *H. pylori* infection.

- Relapse rate of PUD after *H. pylori* eradication (in infected individuals) → 15%

- Relapse rate after treatment with H2antagonists and proton pump inhibitors (PPIs) → 80% to 100%

- Furthermore, *H. pylori* eradication therapy may lead to a permanent cure and therefore eliminates the need for costly, long-term treatment with other anti-ulcer drugs.

**Gastro-oesophageal Reflux Disorder (GORD)**

- Gastric reflux (the retrograde movement of gastric contents from the stomach to the oesophagus) is a normal physiological event and many patients

- Up to 40% in Westernised society may experience symptoms of heartburn at least once a month.

- **Gastro-oesophageal reflux disease (GORD)** occurs when symptoms and mucosal injury develop as a result of excessive oesophageal exposure to gastric reflux.

- GORD is a chronic condition that may have long-term complications if left untreated and has a high rate of relapse following discontinuation of treatment.

- GORD is frequently self-treated with antacids and many patients with mild or sporadic symptoms do not seek help from a medical doctor.

- A number of patients do not experience typical symptoms of GORD (e.g. heartburn, regurgitation) and may present with atypical symptoms such as chest pain, sore throat, hoarseness or pulmonary symptoms.

- The incidence of mortality due to GORD is low (approximately 1:100 000), however it can severely limit the quality of a patient’s life, especially if symptoms are severe and persistent.

- Severe cases of GORD may lead to complications such as oesophageal ulceration, bleeding, perforation, oesophageal stricture and Barrett’s oesophagus (replacement of normal epithelium with columnar epithelium that has a high risk of becoming malignant).

**Risk factors:**

**Reduced sphincter tone:**

- Foods (e.g. chocolate, fatty meals, carminative such as spearmint or peppermint)

- Drugs (e.g. calcium channel blockers, diazepam, theophylline)

- Smoking

- Alcohol

- Hormones (e.g. oestrogen, progesterone)

- Physiologic factors (e.g. prostaglandin, glucagon, vasoactive intestinal peptide)

**Reduced swallowing capacity:**

- Neurological disorders (e.g. stroke)

- Decreased saliva production (e.g. elderly, anticholinergics)
Non-pharmacological Management, GORD:
- Avoiding large meals (eat smaller meals more frequently)
- Elevating the head of the bed (increase oesophageal clearance)
- Avoiding foods that may reduce LOS tone (e.g. chocolate) or that have a direct irritant effect on the oesophageal mucosa (e.g. citrus foods, tomatoes)
- Reducing high fat content in diet (lowers LOS tone and delays gastric motility) and including more protein-rich meals (increases LOS tone)
- Weight reduction in overweight patients
- Cessation of smoking (reduced gastric acid and spontaneous LOS relaxation)
- Reducing alcohol consumption
- Avoiding drugs which may reduce LOS tone (e.g. calcium channel blockers, nitrates) or increase gastric acidity (e.g. aspirin, NSAIDs)

Drug Therapies in GORD & PUD

Antacids
- The antacids have been used for many years in the management of PUD and are available in a variety of combinations of the following antacid ingredients:
  - Aluminum hydroxide / oxide (Mylanta®, Gaviscon®)
  - Calcium carbonate (Andrews Tums®)
  - Magnesium carbonate/ hydroxide / oxide / trisilicate (Mylanta®, Gaviscon®)
- Antacids may also be combined with anti-flatulants (e.g. simethicone), antispasmodics (e.g. dicyclomine) or anti-regurgitants (e.g. alginic acid), however these formulations do not confer any additional efficacy in the healing of ulcers
- Most tablets require chewing before swallowing to ensure complete dissolution of the antacid in the stomach

Mechanism of Action - Antacids
- The antacids act by neutralizing or buffering hydrochloric acid thereby raising the gastric pH
- They are thought to have an additional effect of protecting the gastric epithelial cells by:
  - increasing bicarbonate and mucus secretions
  - inactivating pepsin
  - binding bile salts
  - enhancing gastric microcirculation
- The efficacy of the antacids is dependent on their acid-neutralizing capacity.
- Magnesium and aluminum containing products are the most widely used antacids.
- Magnesium hydroxide is the most potent acid neutralizing compound and has a more prolonged neutralizing effect than the other antacids.
- Regular dosing is required which limits use of these products as long term therapies, or monotherapy in many patients

Adverse Effects - Antacids
The most common adverse effects of the antacids are gastrointestinal and include:
- Diarrhoea (caused by magnesium)
- Constipation (caused by aluminum)
  - Magnesium and aluminum are often used together to minimize these side effects.
  - Aluminium has also be associated with an increased risk of Alzheimer’s disease

Drug Interactions - Antacids
- Can affect the absorption (reduce or delay) and affect bioavailability of some drugs so needs to be taken at least 2 hours before or after (some antibacterials e.g. tetracyclines quinolones – antibacterial; alendronate – bisphosphonate used to treat osteoporosis; amprenavir – antiviral; digoxin interact with Al³⁺ & Mg²⁺– treats heart failure; glucocorticoids – immunosuppressive; phenytoin – anticonvulsant
Can affect the binding of certain drugs e.g. sucrulfate binding to the ulcer crater – cytoprotectant (see discussion later)

- Hypoglycaemic (Oral) drugs (Mg²⁺ can increase the absorption)
- Amphetamines, ephedrine, pseudoephedrine (enhance the effect of these drugs)

**Histamine H₂ Receptor antagonists**

- Cimetidine (e.g. Tagamet®)
- Ranitidine (e.g. Zantac®)
- Famotidine (e.g. Pepcidine®)
- Nizatidine (e.g. Nizac®)

**Indications H₂ antagonists**

- They are indicated for short-term use in the treatment of active PUD as well as for gastro-oesophageal reflux disease (GORD).

**Mechanism of Action**

- Histamine binds to the parietal cells and stimulates the secretion of HCl (aggressive factor)
- The H₂-antagonists inhibit the secretion of gastric acid by blocking of the H₂-receptors on the parietal cells.
- Both basal- and meal-stimulated acid secretion is reduced.
- Although the concentration of pepsin is not reduced, the total amount of pepsin section is decreased because the amount of gastric juice is reduced with the use of the H₂-antagonists.
- Furthermore, an increase in gastric pH leads to a reduction in the activity of pepsin.

**Adverse Effects - H₂-antagonists**

The most common adverse effects of the H₂-antagonists are gastrointestinal or central nervous system-related and include:

- Diarrhoea (uncommon with cimetidine)
- Nausea
- Constipation
- Headache
- Dizziness
- Skin rash (rare)

- Cimetidine has a ↑ incidence of adverse effects. It has a weak antiandrogenic activity and may, rarely, cause gynaecomastia or impotence. The elderly are particularly susceptible to the central nervous system effects of cimetidine that may lead to confusion, restlessness, lethargy or disorientation. Therefore the use of cimetidine in the elderly should be avoided.

**Proton Pump Inhibitors (PPI)**

**Examples:**

- Omeprazole (e.g. Losec®)
- Lansoprazole (e.g. Zoton®)
- Pantoprazole (e.g. Somac®)
- Esomeprazole (e.g. Nexium®)
- Rabeprazole (e.g. Pariet®)

**Indications PPIs**

- PUD, severe erosive oesophagitis from GORD, long term treatment of hypersecretory conditions (Zollinger –Ellison syndrome)
Mechanism of Action PPIs

- The cell surface of the parietal cell contains a H+/K+ ATPase pump (proton pump) which is responsible for the active secretion of acid (H+) out of the parietal cell into the gastric lumen.
- This is the final step in secretion of gastric acid and therefore blocking of the proton pump may produce total inhibition of gastric acid secretion.
- The proton pump inhibitors (PPIs) act by inhibiting the enzyme H+/K+ - ATPase (the proton pump) at the secretory surface of the gastric parietal cells.
- The PPIs form a non-competitive and irreversible bond with the enzyme which produces a profound reduction in gastric acid output that lasts for several days after discontinuation of the drug.
- By reducing gastric acid secretion, the PPIs decrease the irritant and erosive quality of the refluxate, thereby minimising oesophageal damage— and thus this drug class is highly indicated for GORD, as well as for PUD.
- The PPIs are commonly used as part of the treatment regimen for H. pylori eradication therapy as they have been shown to suppress H. pylori infection.
- In addition, treatment with PPIs over a 4-week period produces rapid relief of symptoms and healing of oesophagitis in patients with GORD, however relapse occurs frequently and therefore prolonged therapy may be required in patients to maintain remission.

Efficacy of PPIs

- They are more effective than the H2-antagonists in treating peptic ulcers, although this is more apparent in duodenal ulcers.
- In addition to greater efficacy, the PPIs also provide a more rapid resolution of symptoms (e.g. within 2-4 weeks) than the H2-antagonists (8-12 weeks).
- The PPIs are generally effective in patients who are poorly responsive to H2-antagonist therapy.
- The healing rates of the PPIs are impaired by smoking and continued use of NSAIDs.

Adverse Effects – PPIs

The most common side effects of the PPIs include:
- Diarrhoea
- Headache
- Nausea, vomiting, flatulence
- Abdominal pain
- Sustained reduction in hydrochloric acid production (hypo- or achlorhydria) causes a proportional increase in release of gastrin (hypergastrinaemia) into the circulation. The prolonged use of PPIs in rats has shown an increased risk in gastric carcinoid tumours due to hypergastrinaemia, however extensive and widespread use in humans has failed to provide evidence to support this.
- The use of PPIs in PUD is generally not recommended for periods exceeding 8-12 weeks.

Cytoprotective agents – prostaglandin analogues

Example Misoprostol (Cytotec®)
- Prostaglandin is one of the defensive factors and plays an important role in protecting the gastric mucosa from injury.
- Misoprostol is a synthetic prostaglandin E1 cytoprotective agent.

Indications – Prostaglandin analogues

- Treatment of peptic ulcers and the prevention of gastric ulcers associated with NSAID use

Mechanism of Action – Prostaglandin analogues

- At low doses misoprostol has a cytoprotective effect by increasing bicarbonate and mucus production, stimulating gastric mucosal blood flow and strengthening the mucosal barrier against H+ diffusion.
- At higher doses misoprostol has an antisecretory effect and acts by blocking histamine, pentagastrin and meal-stimulated gastric acid output.
Adverse Effects – Prostaglandin analogues

- Misoprostol is associated with a ↑ incidence of adverse effects compared to the other anti-ulcer drugs
  - Diarrhoea, constipation, abdominal pain, nausea, fatigue, dyspepsia, headache
  - Abortifacient with a stimulant effect on uterine tone and can cause uterine bleeding and miscarriage in pregnant women, therefore its use is restricted in women of child-bearing age.
  - Teratogenic in large doses

Warnings & Contraindications Prostaglandin - analogues

- Can cause hypotension in people with cerebrovascular and coronary artery disease

Cytoprotecitive agents – Sucralfate (sucrose with sulphur and Al(OH)₃

Example

- Sucralfate (Carafate®)

Indications

- Short-term (up to 8 weeks) peptic ulcer treatment and for the prevention of stress-induced ulcers

Mechanism of Action

- In the presence of acid, forms a gel that forms a protective, acid resistant barrier in the ulcer which hastens healing
- Stimulates production of mucous and protective prostaglandins

Adverse Effects

- Constipation, nausea, vomiting, dry mouth, dizziness, back pain, rash

Drug Interactions

- Antacids (reduce effectiveness), some antibiotics digoxin, theophylline, phenytoin (decreased absorption and bioavailability of these drugs – take 2 hours before sucralfate

Drugs used to treat nausea

Antispasmodic - antimuscarinics

Example: Hyoscine (Buscopan®, Kwells®)

Indications

- Travel sickness, gastro-intestinal spasm

Mechanism of Action

- Anticholinergic spasmolytic (competitive antagonist of actions of acetylcholine) at muscarinic receptors

Adverse effects (anticholinergic)

- Dry mouth, thirst, blurred vision, constipation, urinary retention, tachycardia, restlessness and irritability

Dopamine receptor D2 antagonist Prochlorperazine

Indications
For nausea and vomiting due to causes such as migraine, vertigo and Meniere’s disease.
  o Not indicated for nausea associated with travel sickness, nor chemotherapy

Mechanism of Action
  o Phenothiazine derivative that has an inhibitory action on the chemoreceptive Trigger Zone, CTZ and vomiting centre
  o Act as D₂-receptor antagonists

Adverse effects
  o Constipation, dry mouth, sleepiness, dizziness, blurred vision, extrapyramidal effects (Parkinson’s in the elderly and dystonia in younger people)
  o **Dystonia** is a neurological movement disorder, in which sustained muscle contractions cause twisting and repetitive movements or abnormal postures. The disorder may be hereditary or caused by other factors such as birth-related or other physical trauma, infection, poisoning (e.g., lead poisoning) or reaction to pharmaceutical drugs, particularly neuroleptics (antipsychotics). Treatment is difficult and has been limited to minimizing the symptoms of the disorder, since there is no cure available.
  o Drug causes photosensitivity reactions

Warnings & Contraindications
  o CNS depression

**D₂ antagonist also prokinetic - Metoclopramide**

**Indications**
  o Gastro-oesophageal reflux disease (GORD)
  o Diabetic gastroparesis (stomach paralysis)
  o Prevention of nausea and vomiting secondary to cancer drug therapy

**Mechanism of action**
  o Central and peripheral actions in preventing or relieving nausea and vomiting
  o Centrally, blocks dopamine (D₂) receptors in the chemoreceptor trigger zone (CTZ)
  o Peripherally, increases gastric emptying time, reduces reflux from duodenum and stomach into the oesophagus, enhances motility of upper GIT

**Drug Interactions**
  o Additive CNS depressant effect with other CNS depressant drugs (avoid combination)

**Adverse Effects**
  o Drowsiness / sedation / fatigue, dizziness, headache, extrapyramidal symptoms (e.g. acute dystonia, tardive dyskinesia), hypotension, tachycardia

**Warnings & Contraindications**
  o Avoid use in people with phaeochromocytoma
  o Use with caution in people with Parkinson’s, depression
  o Use with caution severe renal impairment
Serotonin antagonists at 5-HT3 receptor – the setrons

Example
- Ondansetron

Indications
- Prevention of nausea and vomiting associated with the use of cytotoxic agents and radiotherapy

Mechanism of Action
- Serotonin antagonists – selective for 5-HT3 receptors found on afferent fibres of vagus nerve in GIT tract and brainstem
- 5-HT released in response to administration of antineoplastic agents cannot bind to the receptors

Adverse effects
- Transient headache, diarrhoea, constipation

Warnings & Contraindications
Used with caution in patients with impaired liver function

References

Additional Resources
- If you find other educationally-useful videos, add them to the Loop / Forums


