Session 08
Drugs Affecting the Blood, Gastrointestinal Tract and Lipid-lowering Drugs
Department of Biosciences
Session Outline

Drugs Affecting the Blood
- Warfarin – actions and adverse effects.
- Anti-platelet drugs and their actions.

Drugs used for the treatment of Gastro-oesophageal reflux, GORD & Peptic Ulcer Disease, PUD
- Proton pump inhibitors, PPI, and H2 antagonists and their mechanism of action.
- Cytoprotective agents and antacids.

Antispasmodics

Actions and adverse effects of anti-emetics

Lipid-lowering Drugs
- Hydroxymethylglutaryl Co-enzyme A Reductase Inhibitors – Statins.
- Fibrates.
- Bile Acid-binding Resins (Sequestrants).
- Nicotinic Acid.
Haemostasis

- Homeostatic mechanism triggers to prevent blood loss when a blood vessel has been injured.
- Haemostasis involves
  - vascular spasm
  - platelet plug formation
  - blood clotting (coagulation = formation of fibrin threads)
- Each of these steps may occur in the absence of vessel damage
  - Blood stasis.
  - Atherosclerotic plaque formation/fissure/rupture.
- Inappropriate blood clotting may continue unchecked, and may occlude blood vessels, blocking blood flow to tissues.
  - May result in ischaemia and tissue death.
Platelet Plug Formation

• Platelet Adhesion
  ➢ Initiated when platelets encounter exposed collagen underlying damaged endothelial cells in vessel wall.

• Platelet Release Reaction
  ➢ Platelets activated by adhesion make contact with each other.
  ➢ Release thromboxane A2 and ADP activating other platelets.

• Platelet Aggregation
  ➢ Activated platelets stick together and activate new platelets to form a mass called a platelet plug, which is reinforced by fibrin threads formed during clotting process.
Blood Clot Formation

- Chain of reactions involving a number of clotting factors.
- Clotting factors exist in inactivated forms in the plasma until activated.
- Leads to the formation of prothrombinase (see common pathway).
- Prothrombinase digests prothrombin into thrombin.
- Thrombin cleaves fibrinogen into fibrin (fibres that hold clot together), and also activates clotting factor XIII.
- Clot eventually dissolved by enzymes that degrade fibrin threads.

(Tortora and Derrickson, 2012, p. 745;)

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Anti-platelet Drugs

- Platelet plug formation with key steps that can be inhibited pharmaceutically to prevent inappropriate activation of the pathway
- These drugs are known as ‘antiplatelet’ drugs
Antiplatelet Agents - Aspirin

- Aspirin irreversibly inhibits cyclo-oxygenase COX enzymes – some of which are required to make thromboxane A2.
- (Thromboxane A2 is a key component in the platelet activation process).
- The effect of aspirin on platelet plug formation is long lasting – only overcome when new platelets have been synthesised.

**Indications**
- Prophylaxis and treatment of transient ischaemic attacks, TIA, and other thromboembolic disorders, post surgical heart valve replacement with anticoagulant therapy.

**Adverse effects** – see session 6 (GIT distress, nausea and vomiting, ulceration and blood loss).
Anticoagulants

- Prevent blood clot formation.
- Have no effect on clots that have already formed.
- Do not repair ischaemic tissue that has been damaged by inadequate blood supply.
- Used prophylactically to prevent new clot formation in patients at risk.
  - Eg. Post myocardial infarct, MI, atrial fibrillation, pulmonary embolism, coronary occlusion.

- Two groups
  - Parenteral (Heparin)
  - Oral (eg. Warfarin)
Warfarin

- Warfarin (Coumadin®), Drug of choice for medium-long term anticoagulation.
- Analogue of vitamin K.
- Prevents/decreases vitamin K dependent synthesis of clotting factors – X, IX, VII and II (prothrombin).
  - Factor VII depleted quickly, others follow
- Warfarin – narrow therapeutic index; Highly protein bound (99%) therefore prone to drug interactions leading to excessive bleeding.
- Adverse effects
  - Mild – easy bruising, poor appetite, nausea, vomiting, abdominal cramps, diarrhoea, hair loss, mild skin rash, itching.
  - Serious – abnormal bleeding, unusually heavy/persistent menstrual bleeding, blood in stools, vomiting of blood, nosebleeds, risk of brain haemorrhage, allergic reaction.
Interactions and Warnings

- Many drug interactions, either increasing or decreasing effect
  - Vitamin K decreases effect of warfarin (implications for dietary advice).
  - Dong quai, garlic, ginger and St John’s Wort increase anticoagulant effect.
  - Ginseng decreases anticoagulant effect.

- Warnings and contraindications
  - Use with caution - hyperlipidaemia, hypothyroidism, elderly.
  - AVOID – in case of bleeding- - aneurysm, cerebrovascular bleeding, surgery, severe trauma, severe uncontrolled hypertension, severe diabetes, vitamin C or K deficiency, severe liver/kidney impairment.

- Contraindicated in early or late pregnancy.

- Regular monitoring of International Normalised Ratio, INR
  - Measure of extrinsic clotting pathway.
Other Treatment of Haemorrhage / reversal of anticoagulation

- Warfarin is discontinued 48 hours in advance of elective surgery.
- Heparin may be given instead, short half-life (compared to warfarin) anticoagulant-effect of heparin is easy to reverse, (eg: using protamine antagonist).
- Mild anti-coagulation is appropriate for surgical operations (to limit clot formation, itself a major cause of complications following surgery), while more significant anti-coagulation would cause excessive bleeding during an operation (which is a potential disaster).
- “spontaneous” haemorrhage, well-defined guidelines for management post-surgery, vitamin K + fresh frozen plasma concentrates (which contain clotting factors).
Thrombolytics

- Dissolve clots that have already been formed.
  - Eg. Streptokinase

- Mechanism of Action
  - Dissolves clots via endogenous fibrinolytic system.
  - Converts plasminogen (found in bloodstream) to plasmin.
    - Plasmin is an enzyme that digests clots.

- Adverse reactions
  - Bleeding, fever, headache, nausea, vomiting, hypotension, arrhythmias, allergic reaction, facial flushing, stomach pain, back ache, bloody stools and urine, constipation, severe head aches.

- Interactions
  - Anticoagulants and antiplatelet drugs – increases haemorrhage risk.

- Contraindications
  - Active internal bleeding, recent surgery or cerebro-vascular accident, CVA, hypertension (HTN).
Disorders of Gastro-intestinal Tract

- Upper GIT
  - Peptic ulcer disease (PUD).
  - Gastro-oesophageal reflux disease (GORD).
  - Nausea.

- Lower GIT
  - Inflammatory bowel disease (ulcerative colitis / Crohn’s disease).
  - Irritable bowel syndrome (IBS).
  - Constipation.
  - Diarrhoea.
Non-pharmacological Management - PUD

- Avoid NSAIDs e.g. aspirin, causative role in peptic ulcers.
- Address underlying social / lifestyle factors e.g. stress.
- Stop smoking.
- Avoid foods that exacerbate symptoms (alcohol).
- Ingest foods that promote healing.

Non-pharmacological Management – GORD

- Avoid large meals (eat smaller meals more frequently).
- Not lying down immediately following a meal.
- Elevating the head of the bed (increases oesophageal clearance).
- Avoiding foods that may reduce lower oesophageal sphincter, LOS, tone (coffee) or irritate mucosa (spice).
- Reducing high fat content in diet (lowers LOS tone and delays gastric motility) and including more protein-rich meals (increases LOS tone).
PUD – Role of *Helicobacter pylori*

- In most people with duodenal and peptic ulcer (NSAID chronic use is also one of the major causative agent, peptic ulcer.) Commensal in people who do not get ulcers – other factors involved in forming ulcers but plays important role.
- 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.
- Recurrence of ulcer (duodenal & peptic)dramatically reduced if *H. pylori* eradicated.
**H. pylori Eradication**

- Examples of 7 day eradication regimens (triple therapy two antibiotics + proton pump inhibitor, PPI):
  - Amoxicillin, clarithromycin, esomeprazole (proton pump inhibitor, PPI).
    - Nexium HP 7®
  - Amoxicillin, clarithromycin, omeprazole (PPI)
    - Klacid HP 7®
GORD

- Pathophysiology, gastric reflux (heartburn, regurgitation, atypical symptoms), chronic → mucosal injury.

- Risk factors: obesity, delayed gastric emptying, increased acid production, agents which irritate oesophageal mucosa, reduced LOS tone, reduced swallowing capacity (elderly at risk).

- Long term complications e.g. replacement of normal epithelium with columnar epithelium (dysplastic and then neoplastic cells).

- Common to self-prescribe OTC, antacids.
Drug Therapies – GORD & PUD

Generally indicated for short term use in PUD & GORD, or in those patients who have not responded to *H.pylori* eradication.

- Antacids
- H$_2$-antagonists
- Proton pump inhibitors
- Cytoprotective agents
Antacids

<table>
<thead>
<tr>
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<th>MECHANISM OF ACTION</th>
<th>EFFICACY OR EXAMPLES</th>
<th>DRUG INTERACTIONS OR CAUTIONS / C/I</th>
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<tbody>
<tr>
<td>Antacids (also see Tutorial Handout)</td>
<td>neutralizing hydrochloric acid, HCl, thereby raising the gastric pH protecting the gastric epithelial cells and duodenal lining</td>
<td>Magnesium Hydroxide, Mg(OH)$_2$, aluminium hydroxide, Al(OH)$_3$, carbonates. With anti-spasmodics etc but no additional efficacy in healing ulcers</td>
<td>absorption (reduce or delay) 2 hours before or after (antibacterials, tetracyclines quinolone; and many more ) Amines enhanced effect; Mg$^{2+}$ affects absorption of some drugs</td>
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### H₂-antagonists

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<td>H₂-antagonists (see Tutorial Handout as well)</td>
<td>Block H₂ receptor on parietal cells with decreased HCl production. Pepsin thus less active, as it is not at its optimal pH</td>
<td>Examples Ranitidine (e.g. Zantac®) Cimetidine (e.g. Tagamet®) Short-term use; efficacy reduced if client drinks alcohol</td>
<td>Adverse Effects – gastrointestinal or CNS related (avoid cimetidine in elderly) Drug Interactions Cimetidine inhibits the metabolism of other drugs by the CYP450 system (increased ADR and toxicities) Less bioavailability of drugs absorbed in acidic environment Warnings in Impaired renal function</td>
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## Proton Pump Inhibitors, PPI

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<tr>
<td>Proton Pump Inhibitors (PPI) (also see tutorial handout)</td>
<td>inhibit the enzyme H+/K+ - ATPase (the proton pump) at the secretory surface of the gastric parietal cells Noncompetitive and irreversible so duration of actions = days</td>
<td>Examples: Lansoprazole (e.g. Zoton®) Omeprazole (e.g. Losec®) Indications. In addition to PUD severe erosive oesophagitis from GORD, long term treatment of hypersecretory conditions (Zollinger – Ellison syndrome). Less efficacy if client drinks alcohol</td>
<td>Gastrointestinal Hypergastrinaemia Achlorhydria Use exceeding 8-12 weeks not recommended</td>
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## Cytoprotective Agents

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</tr>
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<tr>
<td>Cytoprotective agent synthetic prostaglandin E1</td>
<td>At low doses, cytoprotective effect</td>
<td>Example Misoprostol (Cytotec®) – Efficacy in gastric ulcers associated with NSAID use</td>
<td>Cardiovascular and cerebrovascular, Gastrointestinal ADR. Restricted in women of childbearing age</td>
</tr>
<tr>
<td>Sulfated sucrose and Al(OH)$_3$ which also stimulate endogenous protective PG and mucus</td>
<td>In the presence of acid, forms a gel = protective, acid resistant barrier in the ulcer crater,</td>
<td>Example Sucralfate (Carafate®) Efficacy in Short-term (up to 8 weeks)</td>
<td>Gastrointestinal e.g. constipation, back pain, rash Many drug Interactions</td>
</tr>
</tbody>
</table>
Drugs used for peptic ulcers

Entero-chromaffin – like ECL cell produces histamine. Schematic diagram of gastric acid secretion and interrelationship between histamine secretion and the acid-secreting parietal cells. Also shown are the sites where drugs act in treating PUD.

Proton pump inhibitors

H$_2$ antagonist

Misoprostol PG analogue

Sucralfate
Anti-spasmodics

Antispasmodic = agent that stops or prevents spasm of smooth muscle.

• Act in small intestine, large intestine, bladder and uterus
• Usually anti-muscarinic drugs (see Session 10 for mechanism of action).
• E.g. mebeverine (Colac™) used for intestinal smooth muscle spasm and propantheline (Pro-Banthine™) can be used as an adjunct in peptic ulcer disease PUD management (does not cross BBB so vagus nerve action peripherally).
Anti-emetics

- Anti-emetics, adjuncts for combating excessive Nausea and Vomiting (N/V), with chemotherapeutic agents in treating cancer. Corticosteroids (combination chemotherapy) also treat N/V by unknown mechanism of action (MofA)?5-HT receptor turnover.
- Anti-emesis needed in migraine N/V symptoms, drugs act at 5-HT receptors in CNS.
- In the disastrous wake of use of thalidomide as an anti-emetic in the 1960s, drug management of N/V in pregnancy is now avoided (hyperemesis gravidarum requires IV rehydration and perhaps drug therapy). M of A, sedative in CNS.
- Prokinetics e.g. metoclopramide, actions directly on stomach and in CNS. M of A metoclopramide, target dopamine receptors in the chemo-receptor trigger zone CTZ. Extra pyramidal adverse effects rare but include dystonia.
- Ginger not CNS action enhances GIT motility directly at stomach (interacts with Warfarin antiplatelet activity in vitro but clinically needs further testing (Veitch et al, 2014).
Coronary Heart Disease

- Ischaemic heart disease (IHD), imbalance between myocardial oxygen demand and myocardial oxygen supply.
- Myocardial oxygen demand is largely determined by the heart rate, myocardial contractility and left ventricular tension. Myocardial oxygen supply is determined by coronary blood flow and arterial oxygen content.
- Ischaemic heart disease has many clinical manifestations, including stable angina, unstable angina, Prinzmetal’s angina, silent myocardial ischaemia, acute coronary insufficiency and myocardial infarction. Of these, angina is the most frequently encountered symptom.
- Coronary Heart Disease (CHD) is also known as 'ischaemic heart disease', IHD, and is the term that describes what happens when the heart's blood supply is blocked or interrupted by a build-up of fatty substances in the coronary arteries. Over time, artery walls clog with fatty deposits are called 'atheroma' - atherosclerosis.
Lipid Lowering Drugs

- Studies have shown that significant changes in plasma lipid levels, whether by pharmacological or non-pharmacological measures, can:
  - Slow the progression of atherosclerosis
  - Induce lesion regression
  - Lower the incidence of coronary events
    - in patients with pre-existing CHD (secondary prevention)
    - and in patients without evidence of pre-existing CHD, (primary prevention)
  - Reduce the incidence of cardiac mortality (death)
Hyperlipidaemia
Non Drug Measures

- Lifestyle changes form an integral part of the management of patients with hyperlipidaemia.

The principle non-drug measures are:
- Dietary modification
- Weight reduction in the obese
- Reduction in excessive alcohol consumption
- Cessation of smoking
- Exercise
- Reducing stress
Hyperlipidaemia - Drug Therapy

- Drug therapy is indicated in patients at risk of CHD in whom diet therapy alone has been insufficient in lowering lipids to treatment target levels.
- Choice of the most appropriate drug for the management of patients with hyperlipidaemia will depend on the patient’s lipid profile. The four different classes of drugs used in the management of hyperlipidaemia are:
  - HMG-CoA reductase inhibitors (statins)
  - Fibrates
  - Bile acid sequestrants (resins)
  - Nicotinic Acid
# HMG CoA Reductase Inhibitors

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<tr>
<th>Lipid-lowering drug sub-class</th>
<th>Mechanism of Action</th>
<th>Efficacy</th>
<th>Limitations</th>
<th>Adverse Drug Reactions (ADR)</th>
</tr>
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</table>
| HMG CoReductase inhibitors – the – statin drugs | • partially block the endogenous synthesis of cholesterol in the liver.  
• hepatocytes upregulate LDL receptors, promoting the clearance of LDL and VLDL from the plasma. | Clinical Benefits  
Reduces total cholesterol and LDL cholesterol  
Atorvastatin and rosuvastatin also reduce triglyceride levels.  
Slows atherosclerosis with less coronary morbidity and mortality and total morbidity. | Only modest effects on HDL (not a limitation)  
With the exception of atorvastatin and rosuvastatin, effects on triglycerides appear to be modest | Gastrointestinal.  
Rarely at therapeutic doses, hepatotoxicity, myopathy, rhabdomyolysis |
# Bile Acid Binding Resins

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| Bile acid sequestrants       | Interrupt the natural entero-hepatic re-cycling process. Thus decrease plasma cholesterol because bile acids are not reabsorbed. Additional cholesterol is converted to bile acids. Hepatic LDL receptors are upregulated. Cholesterol is taken from the blood to be converted to bile acids. | The average daily dose of cholestyramine is 24g per day (±/− 3 scoops). At these doses, the following alterations in lipids may be achieved:  
  o Decreased LDL cholesterol and total cholesterol  
  o No predictable effect on HDL cholesterol. Adjunct to the statins. Indicated for Pruritis | Compliance (gritty texture & adverse effects)  
Expensive if taken at correct therapeutic doses. Possible increase in triglyceride levels  
Gastro-intestinal (not absorbed systemically so limited ADR) |
## Fibrates

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<td><strong>Fibrates</strong></td>
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<td>The fibrates act at several sites of lipid metabolism: Stimulation of lipoprotein lipase activity, (removal of triglycerides from VLDL cholesterol). Inhibition of lipolysis of stored triglycerides in adipose tissue. Reduction in the uptake of fatty acids by the liver. Decreased synthesis and secretion of VLDL triglycerides</td>
<td>The therapeutic effects may vary from one agent to another within this therapeutic class, however, in general, fibrates: Reduce triglycerides, LDL cholesterol and total cholesterol. Slightly raise HDL cholesterol.</td>
<td>clofibrate cholelithiasis, malignancy. C/I in certain liver diseases and kidney dysfunction. Not given with statins due to increased risk of rhabdomyolysis</td>
<td>gastrointestinal, musculoskeletal pain (less commonly, rhabdomyolysis)</td>
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## Nicotinic Acid

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<td><strong>Nicotinic acid</strong></td>
<td>Inhibition of VLDL (very low density lipoprotein) and a reduction in LDL production. Probable mechanisms: Inhibition of fatty acid mobilisation from adipose tissue Inhibition of the production of triglycerides</td>
<td>There may be a benefit in using nicotinic acid as adjunctive therapy in hyperlipidaemia</td>
<td>As therapeutic dose is 2-6 g per day: adverse effects not tolerated well (non-compliance). Formulations in Australia make it difficult to achieve therapeutic dose (8 to 24 tablets to achieve cholesterol lowering effect)</td>
<td>flushing, itching at therapeutic doses of 2-6 g daily</td>
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Tutorial / Forum Discussion – Drug Diary Session 08

Compile a formative summary for drugs/classes discussed in Sessions 5 to 13. Sessions 6 to 12 can be included in a summative assessment. Session 8 Drugs affecting the Blood, GIT and Lipid-lowering Drugs. For the following drugs/ drug classes list the (i) indications(ii) mechanism of action and efficacy, (iii) contra-indications or warnings or limitations and (iv) adverse drug reactions (ADR) (v) examples. Mark your responses out of 10 marks (2 marks for each section (i) to (v). For Warfarin (v) use the LibGuides eBook by Veitch, Smith, Barnes, Anderson, and Phillipson, (2014) to find other coumarins. For the other drug classes (v) give at least two examples.

- Lipid lowering drugs hydroxymethylglutarylCoA reductase inhibitors - Statins
- Lipid lowering drugs fibrates and bile acid binding resins
- Warfarin and its antidote (antagonist in overdose) – Review session 4 on antidotes
- cytoprotective agents,
- antacids,
- proton pump inhibitors and
- anti-H2 antihistamines.
Acknowledgements and Bibliography


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