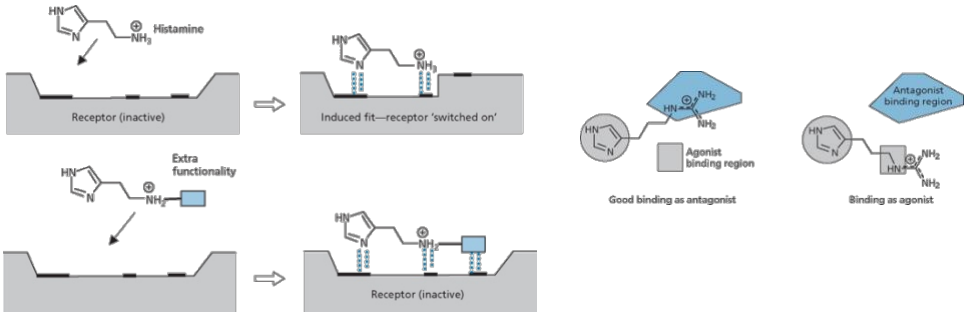
H_2 Antihistamines

- Histamine contains an imidazole group (base) attached to an α amine by a two-carbon ethyl chain –proton is preferentially bonded to the tele-nitrogen over the pi-nitrogen
    - At very low pH –histamine is in di-cationic form (both groups protonated)
    - At phys. pH (7.4) –predominantly mono-cationic form, the α amine is protonated
    - At higher pH –anionic form, proton on α amine lost and eventually proton on imidazole can be removed
- Cimetidine **=** first available H_2 antagonist based on SAR studies conducted using analogues of histamine
    - Was known that everything that stimulates the H_2 receptor had an imidazole ring in its structure
- Design of the antagonist
    - Concept: binding of histamine to an inactive receptor will stimulate/activate it. Adding extra groups will prevent it from being activated (histamine-like compound will still bind):



    - Hundreds of compounds screened, common feature among all was the presence of an imidazole ring
- Functional groups added to histamine structures:
    - N^{α} guanylhistamine → partial agonist –in high enough concentrations, elicits a weak response on its own, but could block the effects of histamine
        - Delocalised positive charge could interact with a site on the receptor that NH_3^+ of the histamine cannot reach
    - Due to the belief that allowing the positive charge to interact with an additional site led to antagonist activity, the side chains joined to the imidazole ring were being extended
        - E.g. isothiourea, extended isothiourea, extended guanidino –all still partial agonists
- **Burimamide:** first pure antagonist to be discovered; developed by increasing chain length (4C) in combination with guanidine analogues (e.g. isothiourea)
    - 100 times more potent than guanylhistamine –proved H_2 receptors exist
    - Not potent enough for oral administration
    - pKa of imidazole ring (7.25) is higher than of histamine (5.7) → ~40% protonated at phys. pH
- Large difference in imidazole ring pKa between burimamide and histamine lead to the development of **thiaburimamide** [by isosteric substitution of sulphur for methylene group] which lowered the pKa of the imidazole ring (6.25) –because the thioether is electron withdrawing (more difficult to protonate)
- **Metiamide**: developed by addition of a methyl (electron donating) to the imidazole ring (pKa=6.8) –this forced the compound into a conformation that was more likely to interact with the receptor (steric effect)
- All were effective anti-ulcer agents but had many side effects (e.g. decreased WBC count) due to the thiourea group –in an attempt to counteract side effects, the thiourea group was replaced for naturally occurring compounds
    - Guanidino analogues had less toxicity but an undesirable partial agonist effect
    - Guanidino group is positively charged and urea is not; hence partial agonist effect of guanidino analogues could be due to the positive charge –removing this charge would give a molecule that was orally active and had good antagonist activity
    - Adding strong electron withdrawing groups removes the charge
- Cimetidine: first H_2 antagonist to contain all the optimal properties –different conformations → E,E and Z,Z caused steric interactions and were disfavoured; E,Z favoured as it has no steric interactions
- Other H_2 antagonists were developed by looking at SAR;
    - Ranitidine: contains a nitroketenaminal group and a furan ring rather than an imidazole ring (not integral to the structure); ~10X more active than cimetidine and less toxic
    - Famotidine –contains a sulonylamidine group and a thiazole ring; 30X more active
    - Nizatidine –contains a nitroketenaminal group and a thiazole ring; 10X more active

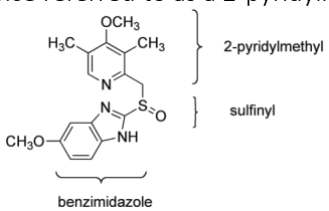
- H_1 vs H_2 antagonists:

H_1	H_2
Lipophilic	Hydrophilic
Non histamine-like	Histamine-like
Bind allosterically	Bind at the active site
Compete for ASP	Compete for ASP
VDW and hydrophobic bonding	H bonding
Cationic at phys. pH (at the α nitrogen)	Cationic at acidic pH (not in the same area of molecule as histamine)

- Histamine binding at the receptor:
  - Ionic interaction (ion-ion bond) between positively charged α amine on histamine and a negatively charged aspartate (Asp98) on receptor
  - Ion-dipole bond between pi nitrogen on imidazole ring of histamine and Arg257 or Tyr182 depending on the type of receptor [essentially act as H-donor site]
  - VDW bonds between imidazole ring and receptor
  - Ion-dipole bond between the tele nitrogen and Asp186 on receptor
- Histamine antagonists binding at the receptor:
  - Ionic interaction between positive imidazole ring and Asp98 on receptor
  - H-bond between alkyl amine and Arg257 or Tyr182 –H donor site
  - VDW bonds with the imidazole ring
  - Ion-dipole bonds between the side chain (protons on guanidino group) and Asp186 on receptor

Proton Pump Inhibitors –Antiulcer Agents

- The proton pump (H^+, K^+-ATPase) is located in gastric parietal cells and responsible for transferring gastric acid from canaliculus (acid-holding chamber network) to stomach lumen. It secretes acid in response to all stimulators [histamine, ACh and gastrin].
- Design of **omeprazole**:
  - First molecule **CMN 131 (pyridyl-2-thioacetone):** originally an antiviral drug –inhibits gastric acid secretion –caused liver toxicity due to thioamide group
  - Modification of thioamide group lead to formation of compound **H 77/67** – still able to inhibit gastric acid (although had effects on iodine uptake in the thyroid)
  - **H 124/26**: conversion of imidazole ring to a benzimidazole
  - **Timoprazole**: oxidation of the thioether to a sulfoxide (metabolite of H124/26) –first orally active, non-toxic drug used for inhibition of gastric acid
  - **Picoprazole:** potent anti-secretory properties over long periods of time –no toxic effects on the thyroid
  - **H159/69**: potent agent but chemically too labile (unstable and ∴ not suitable for formulation into drug)
- Effect of pyridine substituents:
  - Methyl substituents at the *meta* position have a positive inductive effect (weakly electron donating)
  - Methoxy substituents are more effective at *para* position than *meta* position
  - Resonance effect increases electron density on the nitrogen
- The four PPIs currently available are: **omeprazole**, **lansoprazole**, **pantoprazole** and **rabeprazole**
  - All have the same core structure but differ in the substituents on their aromatic rings
  - Behave somewhat like prodrugs –converted to their active forms in strongly acidic conditions (in the canaliculi of parietal cells where HCl is stored)
  - Inactive outside the canaliculi
- The pharmacophore is made up of a 2-pridylmethyl (pyridine ring with methyl at 2'), a sulfinyl (or sulfoxide) and a benzimidazole ring –hence referred to as a 2-pyridylmethylsulfinylbenzomidizaole pharmacophore:



- **Esomeprazole** (Nexium): S-enantiomer of Omeprazole. It has a chiral sulfoxide (stable chiral centre) –tetrahedral sulfur with four different functional groups attached to it
  - S-enantiomer has better potency and a better PK profile
- MOA: benzimidazole acts as a base and gains a proton; nitrogen on pyridine ring acts as a nucleophile and attacks the slightly electrophilic carbon forming an unstable Spiro intermediate (2 conjoined five-membered rings).

    - Spiro intermediate rearranges to form the sulfenic acid intermediate. This can react with the proton pump in two ways;
        - Act directly on the pump to irreversibly inactivate it [non-hydrolysable disulphide bond] OR
        - Be further rearranged to form pyridine sulfenimide which acts on the proton pump via the same mechanism –both pathways involve removal of a water molecule
- Disulphide bond formed between cysteine residues in the luminal vestibule of ATPase: CYS^{813} (most easily reached by PPIs) and CYS^{822} (reached by less reactive PPIs)
    - Disulphide bond forms between sulfur-containing PPI and SH group of the ATPase CYS
    - Bond causes irreversible inactivation of pump = high potency + long duration of action (days)
- PPIs have two basic nitrogens with the potential to protonate at very low pH of the canaliculus (pH 1.5)
    - Pyridine nitrogen: $pKa_1 = 3.83 – 4.53$
    - Benzimidazole nitrogen: $pKa_2 = 0.11 – 0.79$
    - Actual pKa of drugs is determined by the different substituents located on different rings
    - To form the active species, pyridine nitrogen must not be protonated and benzimidazole nitrogen should be protonated (hence require very low pKa)
- There are three cationic forms of the PPI that are possible in very low pH of the canaliculus:
    - Protonated pyridine + free benzimidazole (mono-cation)
    - Protonated pyridine + protonated benzimidazole (di-cation)
    - Protonated benzimidazole + free pyridine (mono-cation) –this form is essential for conducting the PPI activation reaction
- The cationic conjugate acid form of pyridine predominates at pH 1.5 but the unionised conjugate base form is needed to activate the PPI molecule
- The unionised conjugate base form of benzimidazole predominates at pH 1.5 but cationic conjugate is needed to activate the PPI molecule
    - There is generally a very small percentage of molecules in the required form
- Pyridine nitrogen (pKa_1):
    - Ionised:unionised ratio is critical as both conjugates have a role in pump inhibition action (important to have unionised form of pyridine)
    - Because pKa_1 is higher than that of the canaliculus, cationic conjugate acid form will predominate
    - High percentage ionised traps inhibitor in the canaliculus
    - Unionised form is responsible for activating inhibitor via nucleophilic attack at benzimidazole carbon
    - Reactivity of PPIs is directly related to the nucleophilic character of the pyridine nitrogen
- Benzimidazole nitrogen (pKa_2):
    - pKa_2 is lower than the pH of the canaliculus, so the unionised conjugate base form of benzimidazole predominates
    - Benzimidazole nitrogen exists in the cationic conjugate form in a few molecules
    - Cationic centre of these ionized benzimidazole nitrogen atoms pulls electrons from benzimidazole carbon, enhancing its electrophilic character
        - Increased electrophilic character of carbon increases rate of proton pump inhibitor activation through nucleophilic attack by the unionised conjugate of pyridine nitrogen
    - Reactivity of PPIs is directly related to extent of protonation of the benzimidazole nitrogen
- Electron donating groups on pyridine increase percent of pyridine nitrogen ionised but also increase the nucleophilic character of any unionised pyridine molecules. Electron groups on benzimidazole increase the percent of ionisation which increases the electrophilic nature of the benzimidazole carbon.
    - Electron donating groups increase the reactivity of BOTH the pyridine nucleophile and the benzimidazole electrophile and speed up the activation of the PPI molecule –make the pyridine N a better nucleophile and the benzimidazole C a better electrophile
- Omeprazole:
    - Electron donating effect of pyridine 4-OCH_3 (resonance) increases the percent of cationic pyridine and also nucleophilic character of unionised pyridine nitrogen
    - C_3 and C_5 CH_3 groups also enhance nucleophilic character of unionised pyridine through induction
    - C_2 of benzimidazole is made more electrophilic by pi electron donating effect of the 5-OCH_3
    - Acts almost selectively at CYS183
- Lansoprazole:
    - Oxygen of trifluroethoxy ether (OCH_2CF_3) donates electrons through the pi system, increasing nucleophilic character of the unionised nitrogen
    - No electron-donating substituent on benzimidazole to increase electrophilic character of C_2
    - Acts almost selectively at CYS183

- Pantoprazole:
    - Electron donating effect of pyridine 4-OCH_3 increases % of cationic pyridine and also nucleophilic character of unionised pyridine nitrogen
    - Small contribution from pyridine 3-OCH_3 group
    - 5-$OCHF_2$ on benzimidazole decreases ability of the benzimidazole nitrogen to protonate
    - Slow acting and longer t½
- Rabeprazole:
    - C_4-methoxypropoxy group strongly electron donating, very high % of ionised pyridine nitrogen
    - However unionised pyridine nitrogens are very nucleophilic
    - No electron-donating substituent on the benzimidazole to increase electrophilic character of C2
    - Very short t½ (very highly reactive)
- Enteric coating is required as PPI must reach ATPase receptor intact –PPIs are unstable in gastric acid. Sulfenic acid/sulphonamide intermediates are reactive and destructive to proteins. Reactivity is kept under control at higher pH of the intestine and bloodstream –unionised Bz-Pyr conjugate predominates at pH values ≥5.
    - Omeprazole formulated with $NaHCO_3$ is marketed as an immediate release tablet –$NaHCO_3$ increases stomach pH from <2 to 4-5. This prevents protonation of benzimidazole nitrogen required for activation. Hence there is no need for enteric coating and drug is immediately available for absorption in the small intestine.
- Due to the electron withdrawing effects of sulfoxide, there is also an acidic proton (pKa ~12.5) on the benzimidazole ring → ∴ drugs can also be formulated as Na, K or Mg salts by reacting the H with NaOH
- CYP-mediated metabolism is important to the action of all PPIs ***except rabeprazole***
    - CYP2C19 conducts many inactivating reactions on PPI structures
        - O-dealkylation
        - Benzylic hydroxylation
        - Aromatic hydroxylation
    - Most PPIs inhibit CYP2C19, but effect is most pronounced with omeprazole/esomeprazole
    - CYP3A4 is of less importance, mainly involved in oxidation of sulfinyl to inactive sulfone
- Non-CYP metabolic reactions include:
    - Cytosolic oxidation with rabeprazole
    - Phase II sulphate conjugation with pantoprazole
    - Non-enzymatic reduction of sulfinyl (all PPIs)

Helicobacter pylori:

- A non-acid cause of (majority of) gastric ulcers – bacteria that can survive in epithelial layer of the stomach wall –attach to sugar molecule and use mucus layer for protection. They change the pH (neutralise it) and release toxins and irritants that form an ulcer (inflammation and cell damage).
    - Produce large amounts of enzyme urease → catalyses urea to NH_3 and CO_2
    - May also be involved in gastric cancer
- Triple therapy: PPI + 2 antibiotics; usually omeprazole, amoxicillin and clarithromycin OR omeprazole, clarithromycin and metronidazole
    - Clarithromycin inhibits CYP3A4 and to a lesser extent CYP2C19 enhancing PPI activity
    - Eradicates *H. pylori* in 90% of duodenal ulcers and reduces reoccurrence
    - Antibiotics are more effective at higher pH
    - PPIs also have inherent *H. pylori* action

Dyspepsia

- Dyspepsia is a common chronic condition, with a relapsing and remitting nature
- Acid suppression –production of gastric acid of controlled by gastrin, histamine and ACh receptors. When stimulated, these receptors activate proton pumps in the parietal cell.
    - Antacids neutralise gastric acid
    - H_2 antagonists competitively block H_2 receptors on parietal cells
- Prevalence of PPI use has increased significantly, esp. among the older population:
    - Use increased more than 13x in Aus between 1995 and 2006, majority of patients aged >80 yo
- Dyspepsia: range of symptoms in the gastroduodenal region of the upper GI tract, most commonly caused by functional dyspepsia (FD), a relapsing and remitting disorder
    - Criteria for FD: pain/burning in the epigastrium, early satiety, fullness during/after a meal or a combination of these symptoms
    - Global prevalence of FD = 5-11%
    - Symptoms do not reliably distinguish between the organic and functional forms of the disease

    - Symptoms must be chronic, occurring at least weekly and over a 6-month period, in the *absence of an organic explanation*
- Comorbidities:
    - More common in people taking NSAIDS and other drugs such as CCBs and nitrates
    - More common in people infected with H. pylori
    - Association between anxiety and dyspepsia symptoms
    - Strong overlap between IBS, reflux symptoms and dyspepsia –suggests involvement of common genetic or environmental factors
- Symptoms:
    - Heart burn –rising burning
    - Upper abdominal pain, discomfort, soreness and bloating
    - Queasiness and nausea
    - Early satiety –feeling full quickly
    - Excessive burping
- Alarm symptoms:
    - Dysphagia –painful swallowing
    - Odynophagia –difficulty swallowing
    - Hematemesis and/or melena (GI bleeding)
    - Vomiting
    - Weight loss
    - Recent onset
    - Severe symptoms
    - Older age (>55)
    - Inadequate response to treatment
- Symptoms of un-investigated dyspepsia:
    - Ulcer-like dyspepsia: upper abdominal pain (usually relieved by food/antacid) often before meals or when hungry → periodic pain/night pain
    - Reflux-like dyspepsia: heartburn or acid regurgitation
    - Dysmotility-like dyspepsia: nausea/vomiting, abdominal bloating, weight loss or anorexia and pain – aggravated by food, after meals and often relieved by burping.

Causes of dyspepsia:

- Gastro-oesophageal reflux disease (GORD): one of the most common GI conditions in Aus, rising prevalence is most likely due to obesity. Other risk factors: advanced age, male gender, Caucasian ethnicity, high sugar/fat/salt diets and smoking.
    - Often a recurring condition with minority of patients requiring continuous therapy –erosive gastritis usually heals within 8 weeks
    - Typical symptoms: heart burn and regurgitation
    - Atypical symptoms: chest pain, non-specific dyspepsia, nausea, burping, bloating, hoarseness, sore throat and cough
    - In dyspepsia caused by GORD, pain radiates up towards the throat, is relieved transiently by antacids and is precipitated by a meal or by lying down –advice on lifestyle
    - A normal endoscopy does not exclude GORD
    - Timing of PPI administration is important –only effective when proton pumps are active (i.e. after a meal); ∴ best given 30-60 mins before meals
    - Lifestyle: weight loss has a dose-dependent association with symptom reduction –reducing BMI by 3.5 kg/m^2 may result in ~ 40% reduction in risk of frequent symptoms
    - ¾ of people with upper GI symptoms will have no structural organic cause detected via endoscopy for their symptoms.
        - If the main symptom in such patients is heartburn → reflux disease
        - If the main symptom is epigastric pain → functional dyspepsia
- Medication: all NSAIDs are associated with serious adverse GI effects –selective COX-2 NSAIDs generally have a lower risk. Ketoprofen and piroxicam have the highest risk if GI complications, diclofenac and ibuprofen have the lowest –advantage lost for ibuprofen at high doses.
    - Medications that relax the lower oesophageal sphincter (e.g. anticholinergics, theophylline, CCBs, nitrates BZDs) also associated with dyspepsia
    - Oesophagitis may be exacerbated by aspirin, NSAIDs, bisphosphonates, iron salts, potassium chloride, tetracyclines and vitamin C

- Peptic ulcer disease (PUD): H. pylori and NSAIDs (inc. aspirin) are the most important risk factors for PUD and upper GI bleeding. Infection with H. pylori = lifetime risk of PUD (15-20%) and gastric cancer (up to 2%).
    - H. pylori survives in gastric acid by excreting large amounts of urease. This enzyme breaks down any urea in the stomach to ammonia and CO_2.
        - Ammonia neutralises acid found in direct vicinity of bacteria, allowing bacteria to survive
        - CO_2 is absorbed into the bloodstream and then released into the lungs
    - H. pylori breath test involves consuming a drink containing carbon isotope enriched C13 urea. If the bacteria are present – here will be high levels of C13 in the breath after 30 mins (indicates presence of the excretory product; urease)
    - Benefits of eradicating H. pylori:
        - Healing and preventing recurrence of peptic ulcers
        - Managing dyspeptic symptoms in un-investigated dyspepsia
        - Potentially preventing development/recurrence of gastric cancer
        - Curing FD
        - Reducing prevalence of PUD in NSAID users
    - Recommended that H. pylori is tested for and eradicated in patients with GORD who require long term PPI treatment. This is because profound acid suppression may accelerate the progression of H. pylori-induced atrophic gastritis, increasing the potential risk of cancer.
- Functional (non-ulcer) dyspepsia (may be part of a functional syndrome): 70-80% of patients with dyspepsia have no clinically significant findings at endoscopy –classified as functional dyspepsia.
    - Can have a combination of abnormal gastric emptying and increased gastroduodenal sensitivity to mechanical distension or acid
    - Disturbance of sensation overlaps with IBS in ~ 30% of patients
    - Treatment:
        - H. pylori eradication and acid suppression: if one fails, try the other
        - Other options: low-dose TCAs, domperidone, metoclopramide, antacids, sucralfate, antispasmodic agents, cognitive or behavioural therapy and psychotherapy
    - Functional Somatic Syndromes (FSS): characterised by patterns of persistent bodily complains which adequate examination cannot explain
        - Pain of different location (back, head, muscles or joints, chest etc.)
        - Functional disturbance in different organ systems (e.g. palpitation, dizziness, constipation, diahoerra)
        - Complaints associated with fatigue and exhaustion
        - Most common FSS: IBS, chronic fatigue syndrome, fibromyalgia, multiple chemical sensitivity, non-specific chest pain, premenstrual syndrome, non-ulcer dyspepsia, repetitive strain injury
- Alternative therapies: acupuncture, Iberogast (herbal preparation–combination of plant extracts) and peppermint oil combined with caraway oil
- Risks of PPIs:
    - Aspiration of swallowed and enteric flora → pneumonia
    - Reduced inactivation of ingested micro-organisms → gut infections (salmonella, clostridia, giardiasis, etc.)
    - Reduction in calcium absorption → hip fracture
    - Malabsorption of vitamin B12
    - Increased risk of gastric atrophy if infected with H. pylori
    - Acute interstitial nephritis (uncommon)
- Impact of pharmacist-driven protocol to decrease PPI use in non-intensive care hospitalized adults
    - Clostridium difficile: gram-positive, anaerobic bacteria capable of producing spores and cytotoxins responsible for diarrhea. Severe infections may progress to pseudomembranous colitis or toxic megacolon, which may result in sepsis or death. Infections are readily transmitted via the fecal–oral route, and infection rates are increasing in both institutional and community settings.
    - Although antibiotic exposure is a strong risk factor for infections, acid suppressants also plays a significant role (even after single day use). Gastric acid effectively kills C. difficile and neutralizes its toxins. Both histamine H_2-receptor antagonists and PPIs suppress gastric acid production, compromising this barrier to infection. One meta-analysis revealed that PPI use may increase infection risk to a similar extent as antibiotics.
- Continuous low dose PPIs are required for:
    1. People with previous history or at high risk of GI bleeding. This may be made worse/be protective against some medications (e.g. antiplatelet, anticoagulants, NSAIDs).
    2. Established continuing esophagitis