Case Study on Cimetidine (Tagamet)

• 10-20% of adult population might at some stage be affected

• Affect people who are otherwise healthy. Cause illness and pain and can be fatal

• Stomach ulcers are localised erosions of the mucous membrane of the stomach which expose underlying layers of the gut wall to acid and pepsin

• Treatment: prevent acid secretion

• Classic treatment: Antacids

• $\text{NaHCO}_3$, $\text{CaCO}_3$ etc have to be taken in large quantities to have any effect (~60g to get pH 4)

• Surgery. Pre-1970s surgery to remove part of the stomach wall was common in ulcer treatment

• Causes: \textit{Helicobacter pylori} bacterium* and/or NSAIDs such as aspirin

*Marshall and Warren 2005 Nobel prize in medicine
**H₂-Receptor Histamine Antagonists**

- Thought, sight, smell or taste of food causes gastric acid secretion (HCl) and pepsin (a protease) release
- Prior to and during a meal large amounts of acid are released and the pH of the stomach can fall to 1-2

![Secretagogues](image)

**Target: Histamine Receptors**

- Discover specific antagonist of histamine that suppresses gastric acid release by histamine
- Hypothesise that there are two different receptors, H₁ (conventional antihistamines) and H₂
- Target H₂ receptor which was thought to be involved in gastric acid reflux

![Lead Compound](image)

Histamine is generally released as a result of cell damage or infection

Antihistamines used for treatment of hayfever and asthma
Cimetidine

• Smith Kline and French began their cimetidine program in 1964
• One of the earliest and most successful examples of rational drug design, in an era that predated molecular modelling, protein crystallography and genetic engineering
• First data supporting H₂ hypothesis, 4-methylhistamine found to be a highly selective agonist, stimulating gastric acid release

\[
\begin{align*}
\text{Me} & \quad \phi \quad \text{NH}_3 \\
N & \quad \text{NH} \\
H & \quad \text{H}
\end{align*}
\]

Disfavored conformation

• Selectivity observed suggests that histamine must adopt two different conformations for the H₁ and putative H₂ receptor

Cimetidine

• Second breakthrough, \(N^\alpha\)-guanyllhistamine found to be a weak antagonist of gastric acid release (also a partial agonist).

\[
\begin{align*}
\text{HN} & \quad \text{NH}_2 \\
\text{NH} & \quad \text{NH}_2 \\
\text{H} & \quad \text{H}
\end{align*}
\]

Antagonist binding region

• \(H₂\) model developed based on antagonist and agonist binding regions
Cimetidine

Other analogs synthesized

- Led to the development of burinamide, a moderate antagonist with no agonist activity.

- Although burinamide was too weakly active for oral administration in clinical trials, it did prove the existence of H₂ receptors.

- Synthesis

  lysine ethyl ester

  1. Na/Hg, EtOH, HCl
  2. KSCN

  Raney Ni, EtOH
Optimisation of Burinamide

- Imidazole pKa

If one tautomeric form is favoured, then activity could be improved by modifying the structure to favour that form.

- Is burinamide likely to be protonated?

\[ \text{pKa Histamine} = 5.74 \rightarrow \text{Mostly un-ionised at physiological pH} \]
\[ \text{pKa Imidazole} = 6.80 \]
\[ \text{pKa Burinamide} = 7.25 \rightarrow \text{Significantly ionised at physiological pH} \]

- Burinamide is too basic

Optimisation of Burinamide

- Thiaburinamide was synthesised and displayed enhanced antagonistic activity.

- For histamine, it is known that \( N\tau-H \) is the favoured tautomer (more basic).

- \( N\tau-H \) will almost certainly be favoured in thiaburinamide. This structure could be augmented by placing an deactivating group at position 4 of the imidazole ring.
**Metiamide to Cimetidine**

- Metiamide ten times more active than burinamide, but exhibited unacceptable side effects (kidney damage).
- Thiourea group not especially common in human biochemistry; could be causing the problems. Would nowadays be termed a ‘toxicophore’.
- Further motivation to replace the thiourea: excessive conformational isomerism.

![Chemical Structures](image)

**Cimetidine**

- Ideal functional group would be guanidine - Likely to have favourable toxicity profile. However, guanidine analogues already tried and found to be weakly active. Problem must be due to guanidine’s high basicity.
- Appending a cyano or nitro group to the guanidine dramatically attenuates its basicity
- Cimetidine!

![Chemical Structure](image)

- Cimetidine is a strong, selective antagonist of H2 receptors and inhibits gastric acid release. It does not have any serious side effects.
- First marketed in the UK in 1976 as tagamet.
- The world’s first antiulcer drug and the biggest selling prescription product until 1988 (ranitidine)
**Synthesis of Cimetidine**

![Chemical synthesis diagram]

**Cimetidine**

- **Metabolism**

- **Exploiting first in class**

- Conformationally-locked analogues of the cyano-guanidine group

- Sir James Black, leader of the cimetidine program, was awarded the 1988 Nobel prize for medicine for his discovery of ‘receptor selective’ drugs.
**Competitors: Ranitidine**

- GSK drug. Ten times more active than cimetidine, fewer side effects and lasts longer.
- At a glance, appears broadly similar to cimetidine.
- Nitroketeneaminal group replaces cyanoguanidine.
- Furan ring (very unusual to see nowadays) replaces imidazole.
- Furan does not interact with H2 receptor in the same way as the imidazole ring of cimetidine.
- Launched in 1981 as Zantac. By 1988 was the world’s largest selling prescription drug. Earned $6.3 billion profit.

**Famotididine and Nizatidine**

- Famotidine (pepcid), Merck (1985). 30 times more active than cimetidine.
- Lamitidine and loxtidine, 5-10 times more potent than ranitidine and 3 times longer lasting. However, fell out of clinical trials due to toxicity (gastric cancer) in long term animal studies.
Proton pump inhibitors

• Since the 1990s, the H2 antagonists have been largely superseded by a class of compounds called proton pump inhibitors.

• The protons necessary for HCl production in the parietal cells come from water and carbon dioxide, catalysed by an enzyme called carbonic anhydrase.

• Once produced, the protons are exported from the cell using an enzyme complex called the proton pump (or H+/K+ -ATPase).

Proton pump inhibitors

• The proton pump is a fundamentally better strategic target than the H2 receptor. Remember, histamine is just one of several secretagogues.

• The proton pump is downstream of all such targets, operating the final stages of HCl release.

• Omeprazole launched in 1988 by AstraZeneca, quickly became the world’s biggest selling drug.

• Modern treatment for ulcers consists of a PPI plus an antibiotic to kill H. pylori.

• H. pylori causation of ulcers explains the effectiveness of peptobismol (bismuth subsalicylate).