Omeprazole: The First Proton Pump Inhibitor

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Organic Seminar

Michigan State University
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- Gastric acid secretion
- *Helicobacter pylori*, common diseases and treatments
- Proton Pump Inhibitors (PPIs)
  - Development of omeprazole
  - Mechanism of action
  - $P_{ka}$s and their importance
  - Anti-cancer activity and future
- Conclusion
Stomach Cells

- Stomach
- Mucous cells
- Gastric glands
- Blood vessels
- Parietal cell
- Cytoplasm

- ATP is consumed for ion exchange

http://www.britannica.com/eb/art-68634
Mechanism of Proton Transport

- ATP is consumed for ion exchange

Common Disease Related to Inappropriate Levels of Gastric Acid

- **Gastroesophageal Reflux Disease (GERD)**
  - Lower esophageal sphincter closed
  - Lower esophageal sphincter open allowing reflux

- **Peptic Ulcer Diseases**
  - Duodenal ulcer
  - Gastric ulcer
Discovery of *Helicobacter pylori* (Hp)

Nobel Prize in Medicine 2005
- Robin Warren
- Barry Marshall

$\text{(NH}_2\text{)}_2\text{CO} + \text{H}_2\text{O} \xrightarrow{\text{Urease}} \text{CO}_2 + 2\text{NH}_3$

Chronic Peptic Ulcer and Cancer

- Once the bacteria have entered stomach, they cause inflammation and may lead to different diseases.

Chronic Ulcer

Cancer

Helicobacter pylori Infection Globally in 2006

- *Helicobacter pylori* is common and infects half of the world’s population.

![Bar chart showing infection rates in different regions](http://www.worldgastroenterology.org)
Most Common *Helicobacter pylori* Treatments

- **Triple therapy:**
  A proton pump inhibitor + two antibiotics

- **Quadruple therapy**
  A proton pump inhibitor + two antibiotics + bismuth

- **Clarithromycin**
- **Amoxicillin**
- **Bismuth subsalicylate**
Histamine H₂ receptor antagonists

Acetylcholine

Muscarinic antagonists

Gastrin

Histamine

Parietal Cell

Cytoplasm

Lumen

H⁺

K⁺

H⁺-K⁺-ATPase

Proton pump inhibitors

Development of Omeprazole

No effect in humans

Severe liver toxicity

Starting point for the X-Y-Z general structures

Olbe. L, *Proton Pump Inhibitors*, 1999, 3-20
Development of Omeprazole

H 124/26
Leading compound with good anti-secretary effect

H 83/69 (Timoprazole)
Potent anti-secretary but blocking the uptake of iodine

H 149/94 (Picoprazole)
Potent anti-secretary without thyroid effect

Olbe. L, Proton Pump Inhibitors, 1999, 3-20
### Development of Omeprazole

![Chemical Structure of Omeprazole](image)

<table>
<thead>
<tr>
<th>$R_1$</th>
<th>$R_2$</th>
<th>$\Delta pK_a$ (Pyridine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>5-CH$_3$</td>
<td>0</td>
</tr>
<tr>
<td>4-CH$_3$</td>
<td>5-CH$_3$</td>
<td>+0.76</td>
</tr>
<tr>
<td>3-CH$_3$, 5-CH$_3$</td>
<td>5-CH$_3$</td>
<td>+0.94</td>
</tr>
<tr>
<td>4-CH$_3$, 5-CH$_3$</td>
<td>5-CH$_3$</td>
<td>+1.23</td>
</tr>
<tr>
<td>4-CH$_3$, 5-CH$_3$</td>
<td>5-CH$_3$</td>
<td>+1.82</td>
</tr>
<tr>
<td>3-CH$_3$, 4-CH$_3$, 5-CH$_3$</td>
<td>5-CH$_3$</td>
<td>+2.29</td>
</tr>
</tbody>
</table>

Omeprazole

Olbe. L, *Proton Pump Inhibitors*, 1999, 3-20
Development of Omeprazole

H 168/68 (Omeprazole)
Optimal compound

- Prilosec or Losec (Omeprazole) was the world best selling drug by year 2000 (Worldwide sales of US$6.1 b/year)
- Marketed by AstraZeneca

http://www.astrazeneca.com/
Marketed PPIs

- Omeprazole
  - Chemical structure: \( \text{H}_3\text{CO} - \text{N} = \text{S} - \text{O} - \text{N} = \text{C} - \text{CH}_3 \)
- Lansoprazole
  - Chemical structure: \( \text{H}_3\text{C} - \text{O} - \text{CF}_3 \)
- Pantoprazole
  - Chemical structure: \( \text{H}_3\text{CO} - \text{N} = \text{S} - \text{O} - \text{N} = \text{C} - \text{CH}_3 \)
- Rabeprazole
  - Chemical structure: \( \text{H}_3\text{C} - \text{O} - \text{CH}_3 \)
- Tenatoprazole
  - Chemical structure: \( \text{H}_3\text{CO} - \text{N} = \text{S} - \text{O} - \text{N} = \text{C} - \text{CH}_3 \)
Mechanism of Action

Omeprazole

Mechanism of Action of Omeprazole

Methylation on 6th position

- Prevention of formation of the spiro-intermediate by a 6-methyl group

- Strong steric interaction with the imidazole ring
  (revealed by molecular modeling)

Half-lives of PPIs

Half-lives of the inhibitory effect on acid secretion in humans

- 28 Hours for omeprazole
- 46 Hours for pantoprazole

- De novo synthesis of proton pump protein?

Protein pump half-life: 54 Hours

- Reduction of disulfide by an endogenous cellular reducing agents such as glutathione

Labeling and Inhibition of ATPase by Omeprazole

$[^{3}\text{H}]$ Omeprazole

47% inhibition

83% inhibition

KDa

CPM 0 150 300 450 600 0 150 300 450 600

10 min

45 min

Sachs, G. et al, JBC, 1997, 272, 22438-22446
Why PPIs Have Different Half-lives?

46 Hour half-life
Pantoprazole

28 Hour half-life
Omeprazole

Membrane

Shin, J. et al, Gastroenterology, 2002, 123, 1588-1597
Rate Limiting Step

Protonation:

- Pyridine
- Benzimidazole or imidazopyridine

\[
\begin{align*}
X=CH & \quad \text{Omeprazole} \\
X=N & \quad \text{Tenatoprazole}
\end{align*}
\]

Conversion Rates of PPIs at Different pHs

Biphasic rate

Protonation of Benzimidazole and Pyridine

\[
[Bz-Py.H^+] = [Bz-Py] \times 10^{(pKa_1-pH)}
\]

\[
[Bz.H^+-Py] = [Bz-Py] \times 10^{(pKa_2-pH)}
\]

Sachs, G. et al, JACS, 2004, 126, 7800-7811
**pK_a Measurements by UV Spectroscopy**

![Chemical Structures]

X = CH or N

1. \(R_1 X N \text{HSH} \rightarrow \text{MeI, NaOH} \rightarrow R_1 X N \text{SHCH}_3\)

2. \(R_1 X N \text{SHCH}_3\)

3. \(R_1 X N \text{SCH}_3\)

4. \(R_1 X N \text{SCH}_3\)

Measurements by UV Spectroscopy

$pK_a$ Measurements by UV Spectroscopy

$X=$CH or N

Conversion Rates of Methyl-PPIs at Different Medium pH

UV Spectra of $N^1$-methyl Lansoprazole in Different pHs

pK\textsubscript{a} Measurements

- N-methylation and protonated pyridinylmethyl sulfinyl effect

\[
pK_{a2} = 0.7
\]

\[
0.7 - 1.43 = -0.73
\]

pyridinylmethylsulfinyl effect

\[
pK_a = 1.35
\]

\[
1.43 - 1.35 = +0.08
\]

methylation effect

\[
pK_a = 1.43
\]

### Pkₐs of Proton Pump Inhibitors

<table>
<thead>
<tr>
<th>Compound</th>
<th>pKₐ₁</th>
<th>pKₐ₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole</td>
<td>4.06 ± 0.25</td>
<td>0.79</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>3.83 ± 0.15</td>
<td>0.62</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>3.83 ± 0.24</td>
<td>0.11</td>
</tr>
<tr>
<td>Rabeprazole</td>
<td>4.53</td>
<td>0.62</td>
</tr>
<tr>
<td>Tenatoprazole</td>
<td>4.04</td>
<td>-0.12</td>
</tr>
</tbody>
</table>

*P.K. values are calculated for actual measurements and data derived from Sachs, G. et al, *JACS*, 2004, 126, 7800-7811.*
Conversion Rates and $pK_a$ s of Proton Pump Inhibitors

Lansoprazole

\[ \text{Bz} \quad \text{Py} \]

\[ pK_a 1 = 3.83 \]
\[ pK_a 2 = 0.62 \]

Pantoprazole

\[ \text{Bz} \quad \text{Py} \]

\[ pK_a 1 = 3.83 \]
\[ pK_a 2 = 0.11 \]

\[ [\text{Bz-Py.H}^+] = [\text{Bz-Py}] \times 10^{(pK_a 1-pH)} \]
\[ [\text{Bz.H}^+-\text{Py}] = [\text{Bz-Py}] \times 10^{(pK_a 2-pH)} \]

Sachs, G. et al, JACS, 2004, 126, 7800-7811
Conversion Rates of Proton Pump Inhibitors

- Substituent effects on the nucleophilicity of pyridine at $pK_a 1$ (when $pH > 4.0$)
- Conversion rates of PPIs are strongly affected by the second protonation at $pK_a 2$ (when $pH < 4.0$)

Sachs, G. et al, JACS, 2004, 126, 7800-7811
Why PPIs Have Different Half-lives?

Acid Related Activity of PPIs

- **Drug-drug interaction** with other anti-acid drugs

- Since PPIs require stimulation of gastric acid secretion, they are more effective when administered **one hour before breakfast**.

- Protecting PPIs from gastric acid prior to absorption (**formulated with an acid-resistant coating**).
Enzyme-Inhibitor Complex in Acidic Compartment of the Stomach Cell
Release of PPIs in the Body

Acid resistance coat

Esophagus

Duodenum

Small intestine (jejunum and ileum)

pH 2-5

Stomach

pH < 2

pH 6.5-7.5
Other Properties of PPIs

Inappropriate gastric acid levels could be inhibited by PPIs

but:

What other things can PPIs do?
Alternative Uses

Minoxidil tablet
(Hypertension treatment)

(Topical foam)
Other Properties of PPIs

Inappropriate gastric acid levels could be inhibited by PPIs

but:

What is more about PPIs?
Glucose Metabolism in Mammalian Cells

Effect of Medium Acidity on the Viability of Gastric Cancer Cells

Reduction of Cell Viability by Treatment with Pantoprazole

- 0.8 mM PPI for 16 h

Pretreatment of Cancer Cells with Omeprazole

- Melanoma cell line (MelM6)

Pretreatment of Cancer Cells with Omeprazole

Melanoma cell line (MelM6)

Conclusion

- Inappropriate levels of Gastric acid can be inhibited by proton pump inhibitors.

- Different conversion rates of proton pump inhibitors in the body is mostly due to the protonation of benzimidazole ring.

- There might be chances of using current FDA approved drugs for other possible treatments rather than those usages they currently have.

- PPIs are potentially potent anti-cancer agents (treatment or pretreatment of cancer cells) which their anti-cancer activity definitely needs further work.
Works for his heartburn
Works for his budget

Recommend Prilosec OTC for frequent heartburn relief on

- PPI power, affordable relief
- May help your Medicare patients with frequent heartburn save up to $1200 per year

DAY 1

0 HEARTBURN
24 HOURS
1 PILL A DAY

Prilosec OTC

It's possible with Prilosec OTC.

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