PROTON PUMP INHIBITORS

รองศาสตราจารย์ ดร. มุรีรัตน์ ตันติสิระ
ภาควิชาเภสัชวิทยา คณะเภสัชศาสตร์
จุฬาลงกรณ์มหาวิทยาลัย
<table>
<thead>
<tr>
<th>Proton Pump Inhibitors Available in Thailand</th>
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<tbody>
<tr>
<td>Omeprazole</td>
</tr>
<tr>
<td>MUP tab</td>
</tr>
<tr>
<td>- 20 mg</td>
</tr>
<tr>
<td>Capsule</td>
</tr>
<tr>
<td>30 mg</td>
</tr>
<tr>
<td>Trade name</td>
</tr>
<tr>
<td>Generic product</td>
</tr>
<tr>
<td>Injection</td>
</tr>
</tbody>
</table>
Physiology of acid secretion
Physiology of Gastric secretion

- **Antrum (gastrin)**
- **Chief cells (pepsinogen)**
- **Partietal cells (HCl)**
Normal Gastric Protective Mechanisms

Acid and pepsin

Stomach lumen pH 2

Protective factor
Mucous layer thickness (PG dependent)
Cell membrane hydrophobicity
Bicarbonate secretion (PG dependent)
Submucosal blood flow (PG dependent)

Mucous layer
Gastric epithelium
Gastric pH

? HCO₃⁻ HCO₃⁻ HCO₃⁻ HCO₃⁻

HCl HCl
Mechanism of NSAID-Induced Ulcer

Normal Mucosa

Ulcer

Aggressive

Defensive

Acid-peptic activity

? Bicarbonate production

? Gastric blood volume

? Mucus secretion

Suppress endogenous prostaglandins

NSAIDs
Intestinal epithelial cells are continually renewed.

- **Villus Region**: Cell death and sloughing, Turnover time ~ 48-72 hr
- **Crypt Region**: Dividing Cells, Paneth Cells

Normally: # Cells entering villus = # Cells dying
Regulation of acid secretion

- Neurocrine
- Endocrine
- Paracrine
Basolateral membrane

Apical membrane

Gastrin
Histamine
Ach
cAMP
Calcium

Secreting proton pump

cAMP?
Calcium?

resting parietal cell

acid-secreting parietal cell
Proton Pump (H\(^+\), K\(^+\) ATPase) of a Parietal Cell, Embedded in the Apical Membrane

Adapted with permission from Kromer W. Digestion. 1995;56:443-454.
Basolateral membrane

Apical membrane

Gastrin
Histamine
Ach
cAMP?
Calcium?

Secreting proton pump

resting parietal cell

acid-secreting parietal cell
Normal Gastric Physiology

1. STS inhibits gastrin, ECL, parietal cell; gastrin, histamine, acid.
2. Gastrin stimulates parietal and ECL cells.
3. Acetylcholine stimulates parietal cell.

Pharmacodynamics of Proton Pump Inhibitors
PPI Activation

Prodrug → Protonation → Activation (sulfenamide) → Covalent inhibition
<table>
<thead>
<tr>
<th>Generic name</th>
<th>Half-life (h)</th>
<th>Peak effect (h)</th>
<th>Duration of effect (h)</th>
<th>pKa</th>
<th>Bioavailability (%)</th>
<th>Protein binding (%)</th>
<th>Metabolism</th>
<th>Excretion</th>
<th>References</th>
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</thead>
<tbody>
<tr>
<td>Omeprazole</td>
<td>0.7</td>
<td>2</td>
<td>24-72</td>
<td>3.97</td>
<td>30-40</td>
<td>95</td>
<td>Extensively</td>
<td>U = 77;</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>hepatic</td>
<td>F=23</td>
<td></td>
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<td>2.5</td>
<td>24-72</td>
<td>3.96</td>
<td>77</td>
<td>98</td>
<td>Extensively</td>
<td>U = 71;</td>
<td>7</td>
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<td></td>
<td></td>
<td>hepatic</td>
<td>F=18</td>
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<tr>
<td>Lansoprazole</td>
<td>2</td>
<td>1.7</td>
<td>&gt;24</td>
<td>4.01</td>
<td>80</td>
<td>97</td>
<td>Extensively</td>
<td>U = 35;</td>
<td>8</td>
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<td></td>
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<td></td>
<td>hepatic</td>
<td>F=65</td>
<td></td>
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<tr>
<td>Rabeprazole</td>
<td>1</td>
<td>2-5</td>
<td>24</td>
<td>4.9</td>
<td>52</td>
<td>95</td>
<td>Extensively</td>
<td>U = 90;</td>
<td>9</td>
</tr>
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<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>hepatic</td>
<td>F=10</td>
<td></td>
</tr>
<tr>
<td>Esomeprazole</td>
<td>1.3</td>
<td>1.5</td>
<td>24-72</td>
<td>3.97</td>
<td>64</td>
<td>97</td>
<td>Extensively</td>
<td>U = 80;</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>hepatic</td>
<td>F=20</td>
<td></td>
</tr>
</tbody>
</table>

F = faeces; pKa = dissociation constant; U = urine
The recommended dosing schedule for delayed-release PPIs is 30 minutes before breakfast

- food stimulated parietal cell acid secretion
- PPIs bind to actively secreting proton pumps

In a survey of 1046 PCPs across the US

- 36% did not give advice on the time of PPI dosing or advised patients to take a PPI before food

In a survey of 152 omeprazole prescribed in King Chulalongkorn Memorial Hospital (1999)

- 25.17% were prescribed before meal.

Rational Use of Omeprazole in Gastric Acid-Related diseases in King Chulalongkorn Memorial Hospital, 1999.

Chey et al, Am J Gastroenterol 2005; In press

Pezanoski et al, Gastroenterology 2003; 124:A228
**Binding of PPIs to Proton Pump**

<table>
<thead>
<tr>
<th>Drug</th>
<th>cysteine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>321</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>-</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>/</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>-</td>
</tr>
<tr>
<td>Rabeprazole</td>
<td>/</td>
</tr>
</tbody>
</table>

**Recovery of acid secretion in human**

- Omeprazole  27 h.
- Lansoprazole 13 h.
- Pantoprazole 46 h.

**Half life of proton pump = 48 h.**

*Sachs, G.*

*Pharmacotherapy* 2003;23(10 Pt 2):68S-73S
Reversal of omeprazole-and pantoprazole-induced pump inhibition with glutathione in vitro. Inhibited ATPase was isolated from treated rat and the recovery of ATPase activity measured as a function of time of incubation with 10 mM glutathione.
Pharmacokinetics of Proton Pump Inhibitors
All PPIs are prodrugs, acid labile and available as enteric coated delayed-release pellets/tablets.

At duodenum the enteric coated dissolves and unprotonated prodrug is absorbed.

They are highly protein bound, extensively metabolized by cytochrome P 450 and excreted mainly by kidney.
## Pharmacological properties of the different proton pump inhibitors

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Half-life (h)</th>
<th>Peak effect (h)</th>
<th>Duration of effect (h)</th>
<th>pKa</th>
<th>Bioavailability (%)</th>
<th>Protein binding (%)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (? M/L)</th>
<th>AUC&lt;sub&gt;0-24&lt;/sub&gt; (? M*h/l)</th>
<th>Metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole</td>
<td>0.7</td>
<td>2</td>
<td>24-72</td>
<td>-3.97</td>
<td>30-40</td>
<td>95</td>
<td>0.7</td>
<td>1.11 (2.23)</td>
<td>Extensively hepatic</td>
</tr>
<tr>
<td>(20 mg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Pantoprazole</td>
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<td>2.5</td>
<td>24-72</td>
<td>-3.96</td>
<td>77</td>
<td>98</td>
<td>5.73</td>
<td>9.93</td>
<td>Extensively hepatic</td>
</tr>
<tr>
<td>(40 mg)</td>
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<td></td>
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<td>Lansoprazole</td>
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<td>80</td>
<td>97</td>
<td>2.25</td>
<td>5.01</td>
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<td>(30 mg)</td>
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<tr>
<td>Rabeprazole</td>
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<td>2-5</td>
<td>24</td>
<td>-4.9</td>
<td>52</td>
<td>95</td>
<td>0.48</td>
<td>2.2</td>
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<td>(20 mg)</td>
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<td>1.5</td>
<td>24-72</td>
<td>-3.97</td>
<td>64</td>
<td>97</td>
<td>2.4</td>
<td>4.32 (11.21)</td>
<td>Extensively hepatic</td>
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<td>(40 mg)</td>
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</tr>
</tbody>
</table>

F = faeces; pKa = dissociation constant; U = urine
Median and range for CV values for omeprazole and pantoprazole AUC data on day 1 and day 7 of dosing.

Yacyshyn and Thomson
Percentage of claims that are for double doses of the 3 PPIs available in Canada in 2000. Canadian claims for these agents were compiled over and 18-month period up to July 2000.

Yacyshyn and Thomson
Based on ability to metabolise CYP2C19 substrates, individuals can be classified as extensive metabolisers (EMs) or poor metabolisers (PMs).

Distribution of EM and PM genotypes and phenotypes shows wide interethnic differences.

PM
- Caucasians and African American 3-5 %
- Asians 12-25 %

CYP3A4 is more important in PMs.
# Drug Interactions

Metabolic drug interactions: effect of proton pump inhibitors (PPIs) on concomitant drugs

<table>
<thead>
<tr>
<th>Concomitant drug</th>
<th>Esomeprazole</th>
<th>Lansoprazole</th>
<th>Omeprazole</th>
<th>Pantoprazole</th>
<th>Rabeprazole</th>
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<tbody>
<tr>
<td>Autacid</td>
<td>?</td>
<td>Conflicting</td>
<td>None</td>
<td>None</td>
<td>None</td>
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<tr>
<td>Antipyrine</td>
<td>?</td>
<td>Clearance ↓</td>
<td>None</td>
<td>None</td>
<td>?</td>
</tr>
<tr>
<td>Caffeine</td>
<td>?</td>
<td>Clearance ‡</td>
<td>None</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>?</td>
<td>None</td>
<td>Clearance ↓</td>
<td>None</td>
<td>?</td>
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<tr>
<td>Contraceptives(oral)</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>None</td>
<td>?</td>
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<tr>
<td>Cyclosporine</td>
<td>?</td>
<td>Conflicting</td>
<td>Conflicting results</td>
<td>None</td>
<td>?</td>
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<tr>
<td>Diazepam</td>
<td>Clearance ↓</td>
<td>results</td>
<td>Clearance ↓</td>
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<td>None</td>
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<tr>
<td>Diclofenac</td>
<td>?</td>
<td>?</td>
<td>None</td>
<td>None</td>
<td>?</td>
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<tr>
<td>Digoxin</td>
<td>?</td>
<td>None</td>
<td>Absorption ↑</td>
<td>None</td>
<td>Absorption ↑</td>
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<td>?</td>
<td>?</td>
<td>None</td>
<td>None</td>
<td>?</td>
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<td>Glibenclamide</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>None</td>
<td>?</td>
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<tr>
<td>Metoprolol</td>
<td>?</td>
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<td>None</td>
<td>None</td>
<td>?</td>
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<td>Naproxen</td>
<td>?</td>
<td>?</td>
<td>None</td>
<td>None</td>
<td>?</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>?</td>
<td>?</td>
<td>Absorption ↑</td>
<td>None</td>
<td>?</td>
</tr>
<tr>
<td>Phenprocoumon</td>
<td>?</td>
<td>?</td>
<td>Clearance ↓</td>
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<td>?</td>
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<tr>
<td>Phenytoin</td>
<td>Clearance ↓</td>
<td>?</td>
<td>Clearance ↓</td>
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<td>None</td>
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<tr>
<td>Piroxicam</td>
<td>?</td>
<td>?</td>
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<td>?</td>
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<tr>
<td>Tacrolimus</td>
<td>?</td>
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<td>None</td>
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<td>?</td>
<td>?</td>
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<td>None</td>
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<tr>
<td>Warfarin</td>
<td>None</td>
<td>Clearance ↓</td>
<td>None</td>
<td>None</td>
<td>None</td>
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</tbody>
</table>

? = no data available; ↓ = decreases; ‡ = increases
Adverse effects & precaution.

PPIs are generally well tolerated
Side effect < 5 %
Diarrhea, headache are common.
Used with caution in severe hepatic disease
Not recommended in breast-feeding mothers
Clinical Application of PPIs
Acid – related disorders

 manhã

Gastro Esophageal Reflux Disease (GERD)
- non-erosive reflux disease (NERD)
- Erosive esophagitis
- Barrett’s esophagus

Peptic Ulcer disease (PUD)
- gastric ulcer
- duodenal ulcer

NSAID-associated ulcer
DU  - >3 for 18 h/days 4 weeks
GU  - >3 for 18 h/days 8 weeks
GERD - >4 for 18 h/days 4-8 weeks

Patients healed at 8 weeks (%)

![Graph showing healing rates](image)

Bell et al, Digestion 1992; 51(Suppl. 1): 59

Fennerty et al.

New Advances in Immediate Release PPI Therapy, Chicago; May 17, 2005
Supine Position Diminishes Protective Barriers Against GERD

- Gravity-Mediated Drainage
- Esophageal Acid Clearance
- Salivary Flow and Swallowing

References:
### Pathophysiological and pharmacological targets in the treatment of gastro-oesophageal reflux disease.

<table>
<thead>
<tr>
<th>Pathophysiological target</th>
<th>Pharmacological target</th>
<th>Therapeutic agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secretion</td>
<td>Gastric acid secretion</td>
<td><strong>Proton pump inhibitors</strong>, histamine H₂-receptor antagonists</td>
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<tr>
<td>Motility</td>
<td>Oesophageal clearance of refluxed contents</td>
<td>Prokinetics: serotonin 5-HT₄-receptor agonists</td>
</tr>
<tr>
<td></td>
<td>LOS dysfunction</td>
<td>Motilides, CCK₁-receptor antagonists</td>
</tr>
<tr>
<td></td>
<td>decreased LOS tone</td>
<td>GABA-B-receptor agonists, ?-opioid-receptor agonists, muscarinic-receptor antagonists, CCK₁-receptor antagonists, nitric oxide synthase inhibitors, cannabinoid receptor-1 agonists</td>
</tr>
<tr>
<td></td>
<td>enhanced transient LOS relaxations</td>
<td></td>
</tr>
</tbody>
</table>

CCK = cholecystokinin ; LOS = lower oesophageal sphincter.

*Tonini M Giorgio R.D. and Ponti F.D.*

PPIs are the most effective drugs for healing esophagitis

Cumulative esophagitis healing rate (%)

- Delayed-release PPIs
- H₂RAs
- Placebo

Weeks of treatment

n=7635 pts with reflux esophagitis
43 trials, 89 study arms

Chiba et al, Gastroenterology 1997; 112: 1798
Effects of standard doses of current delayed-release PPIs on intragastric acidity

Mean hours pH>4

- Esomeprazole 40 mg: 14.0
- Rabeprazole 20 mg: 12.1
- Omeprazole 20 mg: 11.8
- Lansoprazole 30 mg: 11.5
- Pantoprazole 40 mg: 10.1

n=35
5-way crossover study
Each PPI qd for 5 days

***p<0.001 vs all others

Miner et al, Am J Gastroenterol 2003; 98: 2616

Fennerty et al.
New Advances in Immediate Release PPI Therapy, Chicago ; May 17, 2005
Different proton pump inhibitors compared with omeprazole 20mg daily (odds ratio = 1)
PPI treatment is associated with a reduced incidence of dysplasia in Barrett's esophagus

During 1170 patient-yrs of follow-up, 56 patients developed dysplasia for an annual incidence rate of 4.7%. 

p for log rank test <0.0001

*El-Serag et al, Am J Gastroenterol 2004; 99: 1877*

Katz O.P.
New Advances in Immediate Release PPI Therapy, Chicago; May 17, 2005
<table>
<thead>
<tr>
<th>Indication</th>
<th>Esomeprazole</th>
<th>Lansoprazole</th>
<th>Omeprazole</th>
<th>Pantoprazole</th>
<th>Pabeprazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healing erosive esophagitis</td>
<td>20-40 mg QD</td>
<td>30mg QD up to 8 weeks</td>
<td>20 mg QD x 4-8 weeks</td>
<td>40 mg QD up to 8 weeks</td>
<td>20 mg QD x 4-8 weeks</td>
</tr>
<tr>
<td>Maintenance of erosive esophagitis</td>
<td>20 mg QD</td>
<td>15 mg QD</td>
<td>20 mg QD</td>
<td>40 mg QD</td>
<td>20 mg QD</td>
</tr>
<tr>
<td>Symptomatic GERD</td>
<td>20 mg QD x 4 weeks</td>
<td>15 mg QD up to 8 weeks</td>
<td>20 mg QD x 4 weeks</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Peptic ulcer disease

- Helicobacter pylori
- NSAIDs-induced ulcers
- Acid Hypersecretion
## Differences Between NSAID-Induced Ulcers and Classic Peptic Ulcer Disease

<table>
<thead>
<tr>
<th></th>
<th>NSAID-induced Ulcers</th>
<th>Classic Peptic Ulcer Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Etiology</strong></td>
<td>NSAID use altering gastric mucosa</td>
<td>Mostly Helicobacter pylori</td>
</tr>
<tr>
<td><strong>Site of Damage</strong></td>
<td>Gastric more often than duodenal</td>
<td>Primarily Duodenal</td>
</tr>
<tr>
<td><strong>Pathogenesis</strong></td>
<td>Primarily decreased mucosa defenses (inhibit PG synthesis)</td>
<td>Imbalance of aggressive and defensive factors</td>
</tr>
<tr>
<td><strong>Symptomatology</strong></td>
<td>Rather asymptomatic</td>
<td>Usually pain/dyspepsia</td>
</tr>
</tbody>
</table>
Eradication therapy

(Triple Therapy)

Antisecretary 1 ชนิด ร่วมกับยาต้านจุลชีพ 2 ชนิด เป็นเวลา 7 วัน

antisecretary คือ
omeprazole 20 mg bid ac หรือ
lansoprazole 30 mg bid ac หรือ
RBC 400 mg bid pc

Antimicrobials คือ
Amoxycillin 1,000 mg bid pc หรือ
Clarithromycin 500 mg bid pc หรือ
Metronidazole 400 mg bid pc หรือ
Tetracycline 500 mg qid pc

No major differences in which PPI was used
Decreasing hospitalizations due to complicated gastric and duodenal ulcers in the US: 1988–2001

Triadafilopoulos C..
New Advances in Immediate Release PPI Therapy, Chicago; May 17, 2005
Mechanism of NSAID-Induced Ulcer

Normal Mucosa  Ulcer

Aggressive  Defensive

- Acid-peptic activity
- ? Bicarbonate production
- ? Gastric blood volume
- ? Mucus secretion

Supress endogenous prostaglandins

NSAIDs
### NSAID Use and Increased Risk for Peptic Ulcer Disease in the Elderly

<table>
<thead>
<tr>
<th>Drug</th>
<th>Standard Dose (mg)</th>
<th>Patients(n)</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen</td>
<td>1200</td>
<td>83</td>
<td>2.3(1.8-3.0)</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>50</td>
<td>30</td>
<td>3.8(2.4-6.0)</td>
</tr>
<tr>
<td>Sulindac</td>
<td>300</td>
<td>37</td>
<td>4.2(2.8-6.3)</td>
</tr>
<tr>
<td>Naproxen</td>
<td>500</td>
<td>121</td>
<td>4.3(3.4-5.4)</td>
</tr>
<tr>
<td>Fenoprofen</td>
<td>900</td>
<td>34</td>
<td>4.3(2.8-6.6)</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>20</td>
<td>109</td>
<td>6.4(4.8-8.4)</td>
</tr>
<tr>
<td>Tolmetin</td>
<td>600</td>
<td>21</td>
<td>8.5(4.5-16.1)</td>
</tr>
<tr>
<td>Meclofenamate</td>
<td>200</td>
<td>21</td>
<td>8.7(4.6-16.4)</td>
</tr>
</tbody>
</table>

Griffin et al 1991
GI bleeding risk is related to NSAID dose

<table>
<thead>
<tr>
<th>Ibuprofen dosage (mg/day)</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;600</td>
<td>1.8</td>
</tr>
<tr>
<td>600–1200</td>
<td>3.5</td>
</tr>
<tr>
<td>&gt;1200</td>
<td>3.9</td>
</tr>
</tbody>
</table>

Blot et al, J Epidemiol Biostat 2000; 5: 137

Triadafilopoulos, G.
New Advances in Immediate Release PPI Therapy, Chicago ; May 17, 2005
Rate of gastroduodenal complications with NSAIDs for ≥2 months

- Large, systematic review of RCT, cohort, and case-control studies, and reports (248,890 exposed to NSAIDs)

1 in 1200 - Death
1 in 150 - GI bleeding
1 in 70 - Symptomatic ulcer
1 in 5 - Endoscopic ulcer

Tramèr et al, Pain 2000; 85: 169
Preventive medication in high risk patients

- PPIs
- Misoprostol

Risk factors

- Elderly
- history of PUD
- steroid co-medication
- multiple NSAIDs
Clinical application of PPIs

- GERD
- Eradication of HP
- Preventive medication
- Hypersecretion e.g. Zollinger Ellison syndrome
- Stress ulcer prophylaxis
Criteria for improving the current delayed-release PPIs

- Reduction in individual variability in pharmacokinetics and pharmacodynamics
- More rapid onset of action
- Sustained control of intragastric acidity
- Improved nocturnal acid control
- Dosing independent of meals
- Maintained tolerability and safety of current PPIs
New PPIs

Tenatoprazole/Benatoprazole (TU 199)

- Imidazopyridine derivative
- developed by Mitsubishi Chemical /Phase 3 trial
- Prolonged plasma half life (7 h.)
- 2-4 fold more potent than omeprazole in animal model

Galmiche et al
Aliment Pharmacol Ther 19, 655-662.(2004)
New Pharmaceutical Preparation

Immediate-release omeprazole (IR-OME) powder for oral suspension

- Uncoated omeprazole powder 20 mg or 40 mg
- NaHCO₃ 1680 mg (20 mEq) (to protect the acid labile omeprazole-no enteric coating necessary)
- Reconstituted in 15-30 mL water
- Peach-mint flavor
New Pharmaceutical Preparation

Immediate-release omeprazole in a capsule formulation (Santarus, NDA Filed)
Proposed mechanism of action of IR-OME

- Omeprazole absorption
- Omeprazole
- NaHCO₃
  - NaHCO₃ stimulates gastrin release
  - Omeprazole absorbed
  - Rapid inhibition of acid secretion

Gastrin
New Pharmaceutical Preparation

Immediate-release omeprazole in a capsule formulation (Santarus, NDA Filed)

<table>
<thead>
<tr>
<th></th>
<th>DR-OME 40 mg</th>
<th>IR-OME 40 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction of gastric acid in</td>
<td>No change</td>
<td>-78%</td>
</tr>
<tr>
<td>30 min post-dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cmax (ng/ml)</td>
<td>544</td>
<td>1019</td>
</tr>
<tr>
<td>Tmax (min)</td>
<td>127</td>
<td>25</td>
</tr>
<tr>
<td>AUC (ng.h/ml)</td>
<td>11700</td>
<td>1120</td>
</tr>
</tbody>
</table>
Potential advantages of uncoated PPI-antacid combination (IR-OME)

- Antacid protects the PPI from acid degradation in stomach
  - there is no need for an enteric coating
    + absorption more rapid and predictable
- Immediate therapeutic effect due to acid buffering
- Rapid rise in pH may stimulate gastrin release
  - temporary stimulation of proton pumps
    + improves uptake of PPI by parietal cells independent of food intake
    + more rapid control of acid secretion
Summary

- Delayed-release PPIs
  - acid-labile
  - enteric-coated to protect from acid degradation
  - absorption delayed
  - optimally taken 30 mins before food

- IR-OME
  - peak plasma concentrations within 30 minutes
  - rapid onset of antisecretory action
  - achieves intragastric pH $>4$ for 18.6 hours
24-Hour antisecretory activity of different proton pump inhibitors in healthy volunteers.

Robinson M and Horn J..  
Drugs 2003; 63(24); 2739-3754.
Incomplete heartburn relief in patients with GERD at day 1 of PPI therapy

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Delayed-release PPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 hours</td>
<td>91</td>
<td>69</td>
</tr>
<tr>
<td>Daytime</td>
<td>85</td>
<td>51</td>
</tr>
</tbody>
</table>

17 original articles (18 trials)

n= 215 13980 355 7497

Modified from McQuaid and Laine, Clin Gastroenterol Hepatol 2005; in press

Fennerty et al.
New Advances in Immediate Release PPI Therapy, Chicago; May 17, 2005
Nocturnal acidity on once-daily delayed-release PPIs

- Omeprazole 20 mg qd
- Pantoprazole 40 mg qd
- Lansoprazole 30 mg qd
- Rabeprazole 20 mg qd
- Baseline

Intragastric pH

Tutuian et al, Gastroenterology 2003; 118: A17

Katz P.O.
New Advances in Immediate Release PPI Therapy, Chicago; May 17, 2005
Development of tolerance to single nocturnal doses of H₂RA during twice-daily delayed-release PPI treatment

Time intragastric acid pH<4 (supine) (%)

<table>
<thead>
<tr>
<th></th>
<th>n=40</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>DR-OME 20 mg bid (2 weeks)</td>
<td>30.3</td>
<td></td>
</tr>
<tr>
<td>DR-OME 20 mg bid + ranitidine 300 mg qhs (&lt;1 week)</td>
<td>10.3</td>
<td></td>
</tr>
<tr>
<td>DR-OME 20 mg bid + ranitidine 300 mg qhs (4 weeks)</td>
<td>28</td>
<td></td>
</tr>
</tbody>
</table>

*p<0.05 vs other time periods

Fackler et al, Gastroenterology 2002; 122: 625

Katz P.O.

New Advances in Immediate Release PPI Therapy, Chicago; May 17, 2005
Additional risk factors

- Closed head injury
- Multiple trauma
- Major surgery
- Burns ≥ 30%
- Acute renal failure
- Acidosis
- Coagulopathy
- Thrombocytopenia
- Coma
- Hypotension / shock
- Sepsis

Conrad et al, Crit Care Med 2005; 33: 760
Rationale of pH control in prevention of upper GI bleeding

<table>
<thead>
<tr>
<th>Gastric pH</th>
<th>Physiologic activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥3.5</td>
<td>Decreased incidence of stress-induced bleeding</td>
</tr>
<tr>
<td>≥4.5</td>
<td>Pepsin inactivation</td>
</tr>
<tr>
<td>&lt;5–7</td>
<td>Alterations in coagulation and platelet aggregation</td>
</tr>
<tr>
<td>≥7</td>
<td>Potential decrease in incidence of re-bleeding</td>
</tr>
</tbody>
</table>

Voerder Bruegge et al, J Clin Gastroenterol 1990: 12: S35

Metz D.C.
New Advances in Immediate Release PPI Therapy, Chicago; May 17, 2005
Median intragastric pH in critically ill patients on IR-OME suspension or IV cimetidine

- **IR-OME**
  - 40 mg b.i.d. on day 1, then q.d. via NG tube
- **IV cimetidine**
  - 300 mg loading dose and 50 mg/h infusion thereafter

![Graph showing median gastric pH over trial days](image)

- Patients (n):
  - Day 1: 166, 170, 143, 124, 109, 89, 73, 60, 53, 43, 40, 35, 31, 27
  - Day 2: 174, 175, 157, 162, 103, 88, 78, 70, 59, 51, 46, 39, 33, 28

p<0.001 for days 1–3, p<0.008 for day 14, IR-OME vs IV cimetidine

*Conrad et al, Crit Care Med 2005; 33: 760*

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*Metz D.C.*

*New Advances in Immediate Release PPI Therapy, Chicago; May 17, 2005*
Conclusions

- IV cimetidine is approved for the prevention of bleeding from stress ulcers
- IV PPIs are not approved, although widely used
- Compared with IV cimetidine, IR-OME by gastric tube
  - is at least as effective
  - provides more effective pH control
    + rapid
    + sustained
  - has no increase in nosocomial pneumonia
- IR-OME is the only PPI that is USFDA-approved for the reduction of risk of UGI bleeding
Actions of Gastrin
(on acid secretion)

HCl

Gastric Lumen

ACh

Histamine

'H' Cells

ACh

Gastrin

capillary bed

PS ganglion

Vagus nerve (CN X)

'SST4'

"D" cell

1

2

3

1. ACh activates 'H' cells to secrete histamine.
2. Histamine stimulates parietal cells (H cells) to secrete HCl.
3. Gastrin is released from the G cells and stimulates the secretion of HCl.
4. ACh also stimulates the secretion of Gastrin from the G cells.

The process is further modulated by the vagus nerve (CN X) and SST4 cells in the "D" cell.