Proton Pump Inhibitors

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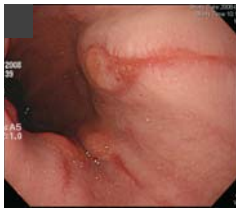
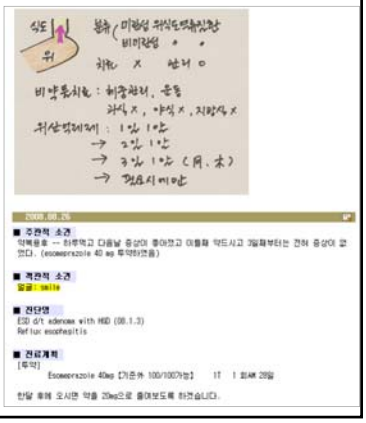
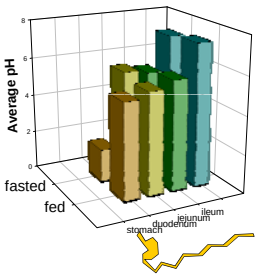
PPI의 마력





Average physiological pHs in GI tract

Site	fasted	fed
Stomach	1.4 - 2.1	3.0 - 7.0
Duodenum	4.9 - 6.4	5.1 - 5.2
Jejunum	4.4 - 6.5	5.2 - 6.2
Ileum	6.5 - 8.0	6.8 - 8.0



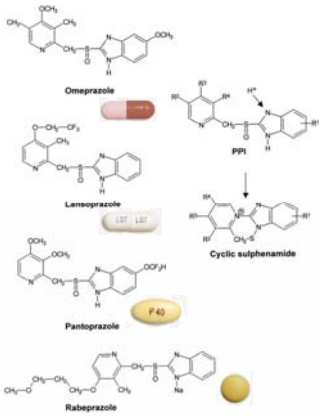
Adapted from Dressman et al. *Pharm.Res 15(1) 11-22(1998)*

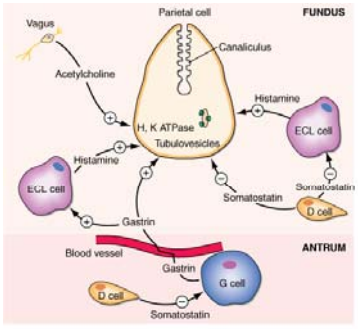
History of gastric acid & PPI

1823	Prout W	Discovery of gastric acid
1836	Schwann	Discovery of pepsin
1938	Komarov SA	Discovery of gastrin
1972	Black JW	Development of H2RA
1979	Olbe	Development of PPI

설상영. 대한소화기학회지 2006;48:4-8

Proton Pump Inhibitors





Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com
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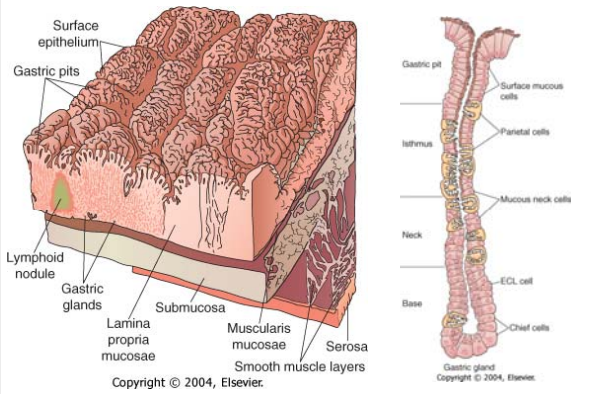
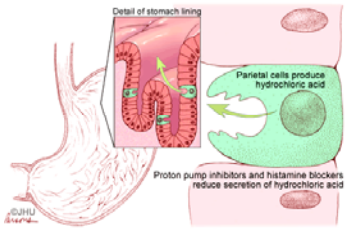
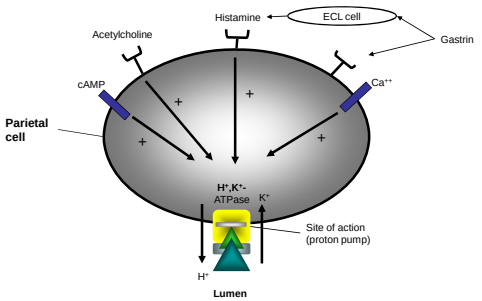


Parietal cells of the stomach



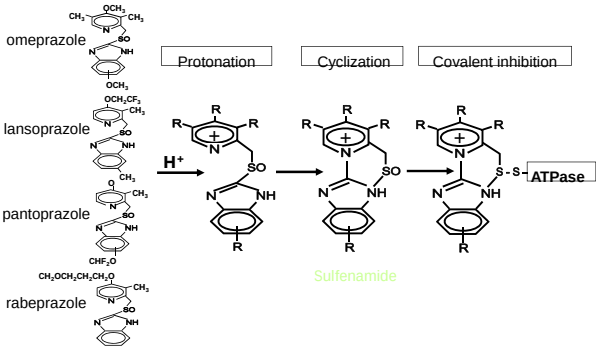
http://pathology2.jhu.edu/beweb/medical.cfm

Site of action of PPIs

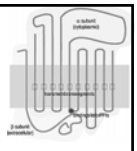


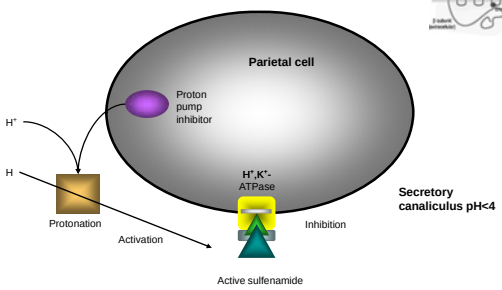
Sachs G. Annu Rev Pharmacol Toxicol. 1995;35:277-305.

Protonation and activation of PPIs



Mechanism of action





Sachs G. Annu Rev Pharmacol Toxicol. 1995;35:277-305.

Proton pump

- The H^+/K^+-ATPase actually consists of two dissimilar subunits.
- The larger of the two, consisting of a chain of 1033 or 1034 amino acids, is the originally identified polypeptide and is referred to as the alpha subunit, or the catalytic subunit. The latter term is in recognition of the fact that this subunit carries out the pumping action of the enzyme.
- The second subunit, the beta subunit is much smaller, consisting of approximately 290 amino acids. The two subunits are found to associated in one-to-one ration and this alpha-beta complex is believed to represent a functional pump unit.

Hubber. APT 1995;9:363-378

Proton pump

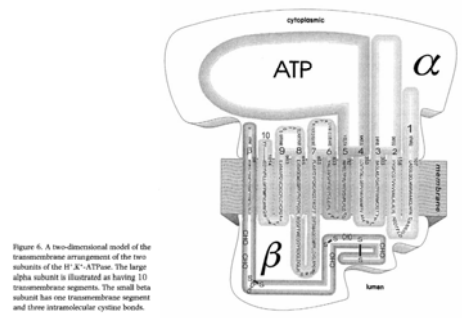
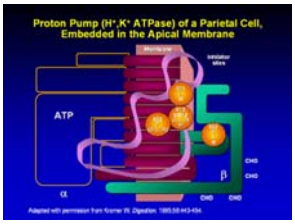


Figure 6. A two-dimensional model of the transmembrane arrangement of the two subunits of the H^+,K^+-ATPase. The large alpha subunit is illustrated as having 10 transmembrane segments. The small beta subunit has one transmembrane segment and three intramolecular cystine bonds.

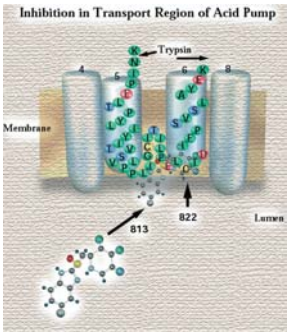
Hubber. APT 1995;9:363-378



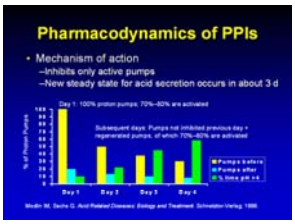
The proton pump inhibitors bind to the cystine residues in the fifth and sixth transmembrane domain of the alpha subunit and bind to either 822 or 813, conferring inhibition of acid secretion.

Omeprazole, rabeprazole, esomeprazole, and lansoprazole bind to other cystine residues which don't contribute to acid inhibition, and we don't know the significance of this binding.

http://www.medscape.com/viewarticle/412819_8

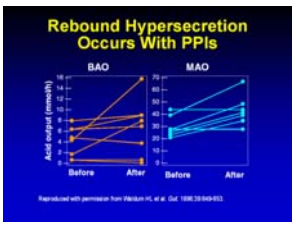


Modlin IM. J Clin Gastroenterol 2004;38:390-402



The important thing with the PPIs is that they only inhibit active pumps. Although we have 100% of proton pumps within our stomach, only about 70% to 80% of them will be activated following a meal, so only that percentage can be inhibited.
The first day, about 80% are inhibited. Then the next day, what you have are the proton pumps that were left over from day one that weren't inhibited, plus the ones that have regenerated, and you can again inhibit 70% to 80% of those, and so forth.Over time, you're inhibiting more proton pumps.
It takes roughly 3 to 4 days to get to a steady state. You can see that in the green, an increase in the percent of time above a pH of 4. PPIs over time only inhibits active pumps.

http://www.medscape.com/viewarticle/412819_8



For several years, people thought that rebound hypersecretion did not occur with the proton pump inhibitors, and that's probably because people looked too soon. These agents have a long duration of action.
Shown here is that, in fact, rebound hypersecretion does occur following discontinuation of a PPI. In this particular study, the authors gave omeprazole, 40 mg a day for 90 days, and then looked at acid secretion, both basal acid output and maximal acid output, 14 days after they discontinued omeprazole. What you see in most patients is a rise in their acid output, indicating rebound in acid secretion..

http://www.medscape.com/viewarticle/412819_8

Proton pump inhibitors inhibit the gastric H+/K+-ATPase via covalent binding to cysteine residues of the proton pump. All proton pump inhibitors must undergo acid accumulation in the parietal cell through protonation, followed by activation mediated by a second protonation at the active secretory canaliculus of the parietal cell.

The relative ease with which these steps occur with different proton pump inhibitors underlies differences in their rates of activation, which in turn influence the location of covalent binding and the stability of inhibition. Slow activation is associated with binding to a cysteine residue involved in proton transport that is located deep in the membrane. However, this is inaccessible to the endogenous reducing agents responsible for restoring H^+/K^+-ATPase activity, favouring a longer duration of gastric acid inhibition. Pantoprazole and tenatoprazole, a novel proton pump inhibitor which has an imidazopyridine ring in place of the benzimidazole moiety found in other proton pump inhibitors, are activated more slowly than other proton pump inhibitors but their inhibition is resistant to reversal. In addition, tenatoprazole has a greatly extended plasma half-life in comparison with all other proton pump inhibitors.

Sachs. Aliment Pharmacol Ther 2006;23(Suppl 2):2-8

Table 1. pK_a values of PPIs[5]

PPI	pK_a1	pK_a2
Omeprazole	4.06	0.79
Lansoprazole	3.83	0.62
Pantoprazole	3.83	0.11
Rabeprazole	4.53	0.62
Tenatoprazole	4.04	−0.12

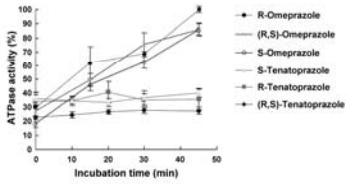
PPI, proton pump inhibitor.

Sachs. Aliment Pharmacol Ther 2006;23(Suppl 2):2-8

Stability of PPI

- omeprazole versus tentaprazole

Figure 2. Stability of proton pump inhibitor inhibition of the gastric H^+,K^+-ATPase. Inhibition by tenatoprazole remains stable in the presence of glutathione whereas ATPase activity returns rapidly with omeprazole as a result of reduction of the disulphide bond coupling omeprazole and the pump.



Sachs. Aliment Pharmacol Ther 2006;23(Suppl 2):2-8

Determination of PPI onset of action

- Product formulation
  - Tablet
  - Capsule
  - Solution
- Activation rate / pH
- Compound's potency and dose

Pharmacokinetics of PPIs

Pharmacokinetic parameters	Omeprazole[a] 20 mg	Pantoprazole[b] 40 mg	Lansoprazole[c] 30 mg	Rabeprazole[d] 20 mg
AUC (μg · h/mL)	0.2–1.2	2–5	1.7–5	0.8
C_{max} (μg/mL)	0.08–8	1.1–3.3	0.6–1.2	0.41
T_{max} (h)	1–3	2–4	1.5–2.2*	3.1†
$t_{1/2}$ (h)	0.6–1	0.9–1.9	0.9–1.6	1
Cl (L · h/kg)	0.45	0.08–0.13	0.2–0.28	0.50
Vd (L/kg)	0.31–0.34	0.13–0.17	0.39–0.46	
Bioavailability (%)	Variable 35 → 65 (with repeated doses)	Constant 57–100	Constant 80–91	
Protein binding (%)	95	98	97–99	95–98
Dose linearity	non-linear	linear	linear‡	linear

Data from References: [a] 2, 7, 10, 15, 16, 18, 27, 62; [b] 2, 6, 11, 15, 101; [c] 2, 8, 10, 12, 13, 16, 92; [d] 4.
AUC, area under the concentration curve; C_{max}, maximum serum concentration; T_{max}, time to maximum serum concentration; $t_{1/2}$, elimination half-life; Cl, drug clearance; Vd, apparent volume of distribution.
*Delayed to 3.5–3.7 with food; †delayed by 1.7 h with food; ‡non-linear in some studies for doses < 20 mg and intravenous administration.

Stedman. Aliment Pharmacol Ther 2000;14(8):963-978

Pharmacokinetics in different conditions

	Omeprazole[a]	Pantoprazole[b]	Lansoprazole[c]	Rabeprazole[d]
Food-effect on absorption	Minimal	Minimal	Delayed absorption, $\downarrow C_{max}$, $\downarrow$F (some studies)	Minimal
Concurrent antacid use	No change	No change	Conflicting results	—
Renal impairment	No change	Conflicting results	Conflicting results	—
Hepatic impairment	$\uparrow AUC$ +++ $\uparrow t_{1/2}$ +++	$\uparrow AUC$ +++ $\uparrow t_{1/2}$ +++	$\uparrow AUC$ +++ $\uparrow t_{1/2}$ +++	$\uparrow AUC$ + $\uparrow t_{1/2}$ +
Elderly	$\downarrow$Cl $\uparrow AUC$, $\uparrow t_{1/2}$	$\downarrow$Cl $\uparrow AUC$	$\downarrow$Cl $\uparrow AUC$, $\uparrow t_{1/2}$	—

Data from References: [a] 6, 16, 18, 23; [b] 6, 11, 15, 18, 19, 22, 23, 26, 62, 92, 101; [c] 6, 8, 12, 16, 17, 20, 23, 25, 92; [d] 24, 111.
AUC, area under the concentration curve; C_{max}, maximum serum concentration; T_{max}, time to maximum serum concentration; $t_{1/2}$, elimination half-life; Cl, drug clearance; Vd, apparent volume of distribution; (−), not tested; (+), small change; (+++), large change.

Stedman. Aliment Pharmacol Ther 2000;14(8):963-978

Drug interactions

CYP 450 enzyme/drug tested	Omeprazole*	Lansoprazole*	Pantoprazole*	Rabeprazole*
CYP 1A2				
Theophylline	No interaction	↓↑Cl	No interaction	No interaction
Caffeine	↑Cl*	—	No interaction	—
CYP 2C9				
Phenytoin	↓Cl (by 15–20%)	No interaction	No interaction	No interaction
S Warfarin	↓↑Cl (↓%)	No interaction	No interaction	No interaction
Carbamazepine	↓Cl	—	No interaction	—
Diclofenac	—	—	No interaction	—
Tolbutamide	↑AUC (by 10%)	—	—	
CYP 2C19				
Diazepam	↓Cl (by 26–94%)	No interaction	No interaction	No interaction
Mephenytoin	↓Cl	—	No interaction	—
R warfarin	↑concentration ×2	No interaction	No interaction	No interaction
CYP 2D6				
Debrisoquine	No interaction	—	No interaction	—
Propranolol	No interaction	No interaction	—	—
Metoprolol	No interaction	—	No interaction	—
CYP 3A4				
Nifedipine	↓Cl	—	No interaction	—
Cyclosporin	No interaction	—	—	—
Quinidine	No interaction	—	—	—
Lignocaine	No interaction	—	—	—
Contraceptives	No interaction	↓effect on ovulation	No interaction	—
Erythromycin	No interaction	—	—	—

Data from References: * 30, 31, 39–42, 44, 45, 112; † 18, 30, 31, 37, 38, 40, 46; ‡ 18, 19, 30, 31, 47, 48; ¶ 4, 43, 49, 51, 52.
CYP, Cytochrome P450; Cl, drug clearance; AUC, area under the concentration curve; (–), not tested; (↓), result not clear; *, in high doses or in CYP 2C19 poor metabolisers.

Stedman. Aliment Pharmacol Ther 2000;14(8):963-978

PPI with sodium bicarbonate?

Table 3. Inhibitors of Gastric Acid Secretion Approved for Use by the Food and Drug Administration (FDA).*

Generic Name	Brand Name	Standard Dose†	Most Common Side Effects‡
Histamine$_2$-receptor antagonist			Headache, diarrhea, dizziness, fatigue, confusion
Cimetidine§	Tagamet¶	400 mg twice daily	
Famotidine§	Pepcid¶	20 mg twice daily	
Nizatidine§	Axid¶	150 mg twice daily	
Ranitidine§	Zantac¶	150 mg twice daily	
Proton-pump inhibitor			Headache, diarrhea, constipation, abdominal pain
Omeprazole§	Prilosec¶	20 mg daily	
Pantoprazole§	Protonix	40 mg daily	
Esomeprazole	Nexium	40 mg daily	
Lansoprazole	Prevacid	30 mg daily	
Omeprazole with sodium bicarbonate	Zegerid	40 mg daily	
Rabeprazole	Aciphex	20 mg daily	

* With respect to safety during pregnancy or lactation, omeprazole is a category C drug (no adequate studies or adverse fetal effects in animals). All other drugs are category B drugs (animal studies demonstrate no risk; no human studies).
† All doses are those commonly prescribed for histamine$_2$ receptor antagonists or approved by the FDA for proton-pump inhibitors in the treatment of esophagitis.
‡ The most common side effects (per package inserts and clinical experience) are listed for each therapeutic class, although none of these effects occurred significantly more frequently with drug than with placebo in controlled clinical trials.
§ This drug is available in a generic form.
¶ This drug is available over the counter without a prescription.

Kahrilas. N Engl J Med 2008;359:1700-7.

Relative potency of PPI – metaanalysis

- Based on the mean 24-h gastric pH, the relative potencies of the five PPIs compared to omeprazole were 0.23, 0.90, 1.00, 1.60, and 1.82 for pantoprazole, lansoprazole, omeprazole, esomeprazole, and rabeprazole, respectively.
- Compared with healthy volunteers, patients with GERD needed a 1.9-fold higher dose and Helicobacter pylori-positive individuals needed only about 20% of the dose to achieve a given increase in mean 24-h intragastric pH.

Kirchheiner. Eur J Clin Pharmacol 2009;65:19–31