Evolution of antisecretory agents

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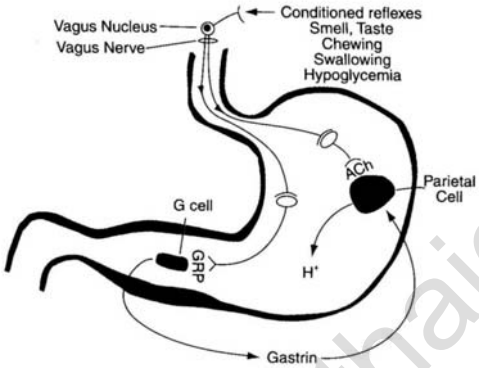
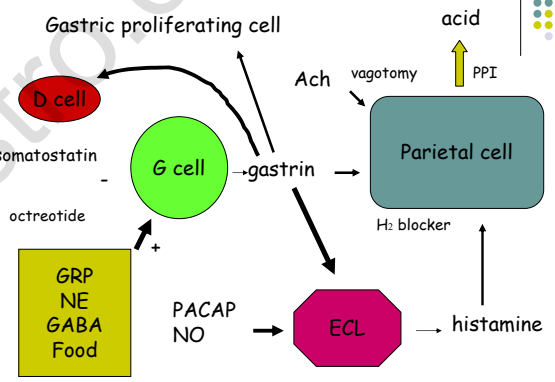
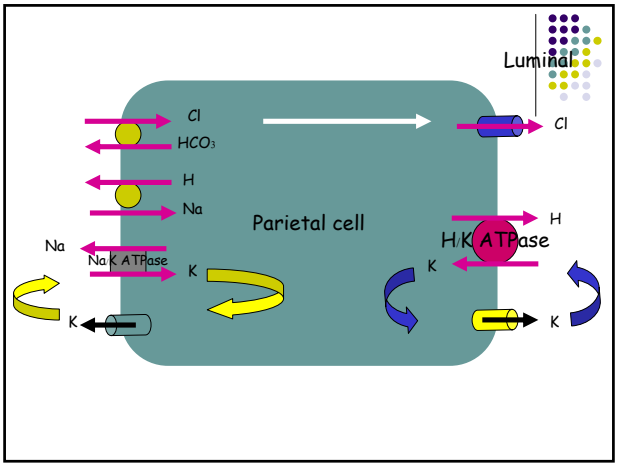
History

- 1823- Prout discovered gastric hydrochloric acid
- 1875- Heidenhain and 1893- Golgi identified oxyntic gland parietal cells as the gastric acid secretory cells







Antacids and anticholinergic drugs

- Long ago, people with an upset stomach commonly ingested powered shells (CaCO3) to alleviate the discomfort.
- Later on, sodium bicarbonate, aluminum hydroxide, magnesium hydroxide as well as calcium carbonate were used as an antacid in either single or combined preparation.
- Effective time is too short.

Antacids and anticholinergic drugs

- To prolong the effect of antacids, anticholinergic drugs, such as propantheline bromide and benactidine methobromide, have been concurrently administered to delay gastric emptying.
- Anticholinergics can also inhibit acid secretion by themselves.
- Limitation- anticholinergic adverse effects.

H2 receptor anatagonists

- 1972- Black and colleagues developed first H2 receptor antagonist, burimamide, followed by metiamide.
- 1975- Brimblecombe and colleagues developed cimetidine.
- By modifying the chemical structure of cimetidine, the potent H2R antagonists ranitidine, famotidine, and nizatidine were all developed.

H2 receptor anatagonists

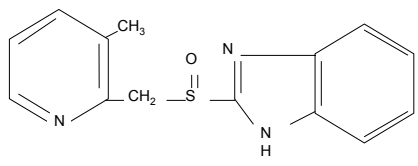
- Cimetidine strongly inhibits cytochrome P450 (CYP) enzymes, particulary CYP3A4.
- Caution in being used with warfarin and diazepam, that are metabolized by this enzyme.
- Ranitidine can weakly inhibit cytochrome P450 as compared to cimetidine.
- Among H2R antagonists, there is no common chemical structure to determine their pharmacologic property.

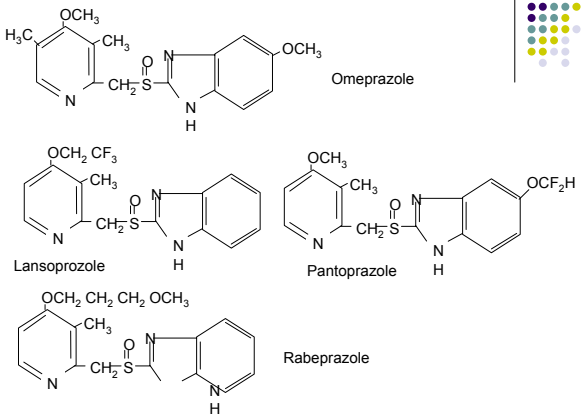
H2 receptor anatagonists

- Little effect on daytime acid control, despite marked suppression of nocturnal acid output.
- Evoke rapid tolerance during therapy.
- Tolerance does not depend on over-expression of H2R, but rather, appears to be related to up-regulation of other pathways that elevated cAMP levels in parietal cells.
- Acid rebound after withdrawal.

Proton pump inhibitors

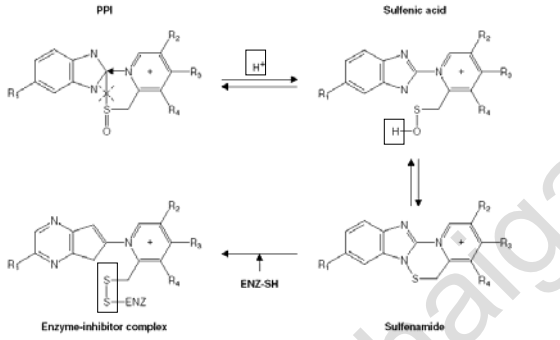
- 1981-2: AB Hassle Company in Sweden accidentally discovered that benzimidazole derivatives could potently inhibit gastric acid secretion in rabbit or guinea pig isolated gastric glands stimulated by dibutyryl-cAMP.
- After that, first PPI, omeprazole, was discovered.
- New PPIs- modification of omeprazole structure but share a common benzimidazole ring.



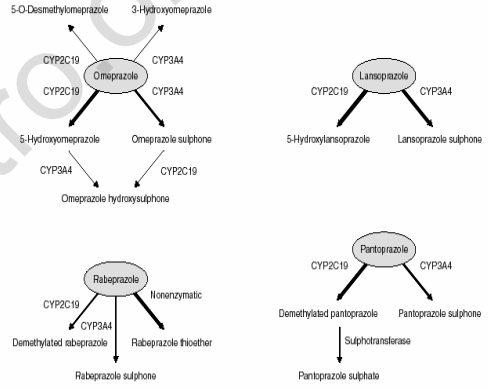


PPIs- pharmocokinetics

- Substituted benzimidazoles with alkaline properties
- Absorbed at the small intestine
- Metabolized in the liver (CYP2C19 and CYP3A4)
- Target at the H/K ATPase molecule on the luminal side of the canaliculi : covalently bound
- PPI: a precursor of thiophilic sulphenamides
- Transformation is pH-dependent and occurs within the parietal cell (active metabolite)
- This binding takes place at a high velocity at pH 1.



Gibbons TE and Gold BD. Pediatr Drugs 2003;5:25-40.



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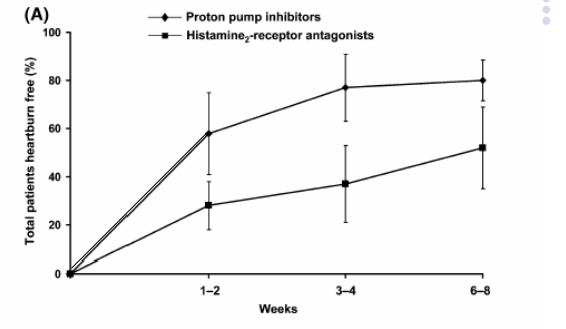
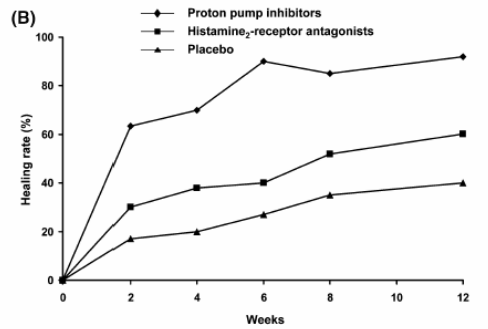
Efficacy



Chiba N, et al. Gastroenterology 1997;112:1798-810

Efficacy



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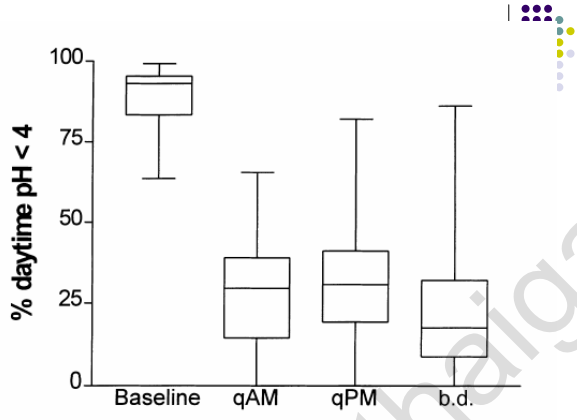
Efficacy

- Be accepted higher compared to H_2RA
- PPIs (including esomeprazole) probably have similar miligram potencies in treatment of various GI diseases.
- Differences are based on:
  - Onset of action
  - Side effect and drug interaction: Rabeprazole
  - Administration e.g.
    - IV vs. Oral
    - Tablet vs. Capsule
    - Size of granules (small and fast disintegrating)

Limitation of PPIs

- Acid control: Daytime > Nighttime
- Nocturnal gastric acid breakthrough
- Interindividual / Intraindividual variation
- Carcinoid tumor- in long term therapy (experimental model)



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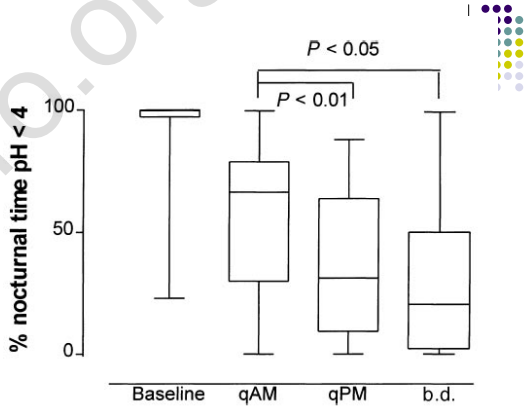

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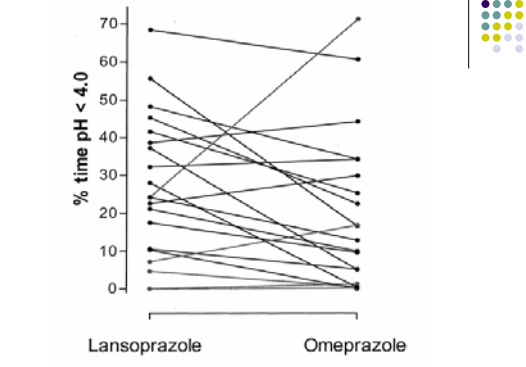

Katz PO, et al. Aliment Pharmacol Ther 2000;14:709-14.

Esomeprazole

- Latest PPI
- S-isomer of the omeprazole
- S-isomer- less metabolized in the liver (CYP3A4 > CYP2C19) compared to R-isomer (omeprazole) -> higher plasma level
- However, the recommended dose in adults is 40 mg which is higher than omeprazole (20 mg).

Limitation of PPI use in children

- The majority of published studies have been performed in adults rather than children.
- Lack of evidence-based guidelines on the use of PPIs in pediatric populations.
- Different pharmacokinetics
  - Maturity of P450 enzymes according to various age groups
  - Immaturity of parietal cells and a relative achlorhydria
  - Different gastric emptying time and intestinal transit time