1. Efficacy and proved safety of PPI (in adults). The legend.
2. Over-prescription of PPIs, focus on infants.
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5. Suggestions by Eric Hassall on PPI use in infants.

The Niagara Falls in the stomach

![Diagram of gastric mechanism]

The mechanism of PPIs

![Diagram of PPI mechanism]

Efficacy of PPIs and their superiority over H2RA

No tachyphylaxis

“Tolerance that occurs with H2RAs does not occur with PPIs.”


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A great success!

Saved lifes.

Reduced incidence of GI surgeries.

Sales totalling $13.6 billion worldwide in 2009.

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Efficacy and short-term use safety of PPIs in pediatric patients
An important contribution made by Drs. Robert and Susan Baker

Clinical Results From a Randomized, Double-Blind, Dose-Ranging Study of Pantoprazole in Children Aged 1 Through 5 Years With Symptomatic Histologic or Erosive Esophagitis

Robert Baker, MD, PhD, V. Marc Teno, MD, Julee Young, MD, Susan Seidner Baker, MD, PhD, Halina Li, MD, MS, Wenshong Wang, PhD, Natalie Roth, BS, RN, Mary K. Maguire, PharmD, and Collin M. Connor, MD


1. Effect and proved safety of PPI (in adults). The legend.
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PPIs are the second most commonly prescribed drug class in US. Williams et al., 2009 Drug Discovery Today, 14:477

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A very recent report in Clinical Gastroenterology and Hepatology

Clinical Gastroenterology and Hepatology

Volume 10, Issue 1: Pages 84-82

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5. "...between 53% and 69% of PPI prescriptions are for inappropriate indications."

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2/6/2012
From 1999 to 2004, there was a 7-fold increase in PPI prescription.

One of the PPIs, available in a child-friendly liquid formulation, saw a 16-fold increase in use during that 6-year period. Treatment with PPIs is no better than placebo.

Many infants spit up on a daily basis—some 40% to 70%. Many infants are irritable or have "unexplained crying".

GERD

Over-prescription of PPI unnecessarily removes/affects

An important defense against infection.
Protein digestion by pepsin.
Nutrition absorption (Ca, Fe, Mg, VB12)
Milk coagulation by acid/pepsin.
AND adds side effects.

Once activated (in the form of sulphenamide), omeprazole can “react with SH groups in the acidic stomach contents, and with SH groups in the neutral contents of the intestine.”

Abundant rearrangement products of omeprazole at acidic environment
If the stomach has a pH so much lower than the rest of the body, does not PPI only trapped at the stomach?

No.

Omeprazole accumulates in organs other than the stomach

Localization of omeprazole and metabolites in the mouse

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*Department of Pharmacology, AB Hasle, Möln达尔, Sweden
**Department of Toxicology, AB Astra, Södertälje, Sweden

The mean plasma concentration and SD of omeprazole in the mouse after intravenous administration of 10 mg/kg, omeprazole at a dose of 15 mg/kg, n = 4

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Control</th>
<th>Low</th>
<th>Medium</th>
<th>High</th>
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</thead>
<tbody>
<tr>
<td>16</td>
<td>0.077 ± 0.01</td>
<td>0.032 ± 0.00</td>
<td>0.004 ± 0.00</td>
<td>0.007 ± 0.00</td>
</tr>
<tr>
<td>72</td>
<td>0.061 ± 0.01</td>
<td>0.034 ± 0.00</td>
<td>0.01 ± 0.00</td>
<td>0.01 ± 0.00</td>
</tr>
</tbody>
</table>

M.d. = Minimum detectable concentration.

Omeprazole cause gastric carcinoids in rat.


Omeprazole cause gastric carcinoids in rat.


It is unethical to perform a similar controlled study with patients.

Side-effects due to inhibition of CYP2C19

PPIs are removed in the liver by cytochrome P450: CYP2C19 and CYP3A4.

CYP2C is also responsible for the metabolism of other drugs: diazepam, S-warfarin, and tolbutamide, etc.

Clopidogrel: prodrug used to inhibit platelet aggregation. After absorption, it requires activation by CYP 2C19, before becoming active against platelets.
Previous research of PPI effect on lysosomal enzymes


No effect observed!

All studies performed with liver!!!
Liver is where PPIs are removed.

A discovery by accident: PPIs are activated at pH5!

At pH5:
PPI + Peptide-SH

At pH5:
PPI-S-S-peptide

Mass spectrum of the omeprazole-peptide adduct

I wanted to do the experiment at pH2, but ....

Omeprazole-laminin (925-933) adduct was produced at pH5:

Collision-induced dissociation mass spectrum of the omeprazole-peptide adduct

How did it happen?
PPI is active at pH5?
PPI react with peptides other than the proton pump?

Given that the pKa of the PPIs are in the range of 4-5,
The following reaction is expected at pH5:

PPI + Peptide-SH

Activated PPI

PPI-S-S-peptide adduct

This reaction is rather complete, and removing activated PPI, and shifting the balance of the above reactions

Starting material:

Omeprazole

Starting material:

Laminin (925-933)

Product from

Omeprazole and

Laminin (925-933)

The total ion intensities of each molecule were determined using the Bayesian peptide reconstruction module provided in the Bioinfomatics extension of the Analyst QS software version 2.0

PPI + Peptide-SH

PPI-S-S-peptide

PPI 45.5

0 100 200 300 400 500 600 700 800

Intensity (a.u.)

R S G I Y P [D C] Omeprazole

PPI 29.7

0 100 200 300 400 500 600 700 800

Intensity (a.u.)

R S G I Y P [D C] Omeprazole

PPI 45.5

0 100 200 300 400 500 600 700 800

Intensity (a.u.)

R S G I Y P [D C] Omeprazole

PPI 29.7

0 100 200 300 400 500 600 700 800

Intensity (a.u.)

R S G I Y P [D C] Omeprazole
pH5 means everywhere in our body:

Lung, kidney, skin, vagina, and importantly lysosomes in every cell!

Mice treated with PPIs

Stomach, Liver: no inhibitory effect observed with any of those three PPIs.

However, in the spleen:

- pH5: 0, 0.57, 2.85
- pH7: 0, 0.57, 2.85

Lansoprazole and pantoprazole also inhibit lysosomal enzymes

Summary of our findings

PPIs are readily activated at pH5.

In vitro and in vivo experiments indicated that PPIs inhibited lysosomal enzymes.

The PPIs effect on lysosomal enzyme is organ/cell specific.

Difference exist among different PPIs.

Lysosomes play key roles in antigen presentation and cytotoxic T lymphocyte function.

By interfering with patient immune system, PPIs may increase the risk of tumorigenesis and infectious diseases.

Spitting up, occasionally irritable/crying, usually consolable

Reassurance about the benign natural history of infant regurgitation

Long-lasting intractable crying, with rejection of the bottle or breast, arching or screaming

non-pharmaceutical measures should be the first approach

Non-analytic, non-nutritive soothing maneuvers

Position and diet often work

Does the child relapse at weaning off PPI?
H2RA and corporectomy also caused carcinoids, therefore "PPI causing carcinoid" was ignored.