PATHOGENESIS AND MANAGEMENT OF GERD

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International Congress on Natural Medicine
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Heartburn

Sleep disturbance

Chronic cough

Asthma

Barrett’s Esophagus

Globus

Enamel erosion

Esophageal Stricture
WHY IS GASTROESOPHAGEAL REFLUX DISEASE (GERD) IMPORTANT?

• ~ 20% U.S. adults experience symptoms weekly – heartburn, chest pain, etc.
• ~ 60% annual prevalence in U.S. adults
• Directly linked to obesity
• U.S. annual direct cost of treatment > $9 billion (PPI market > $13B annually)
GASTROESOPHAGEAL REFUX DISEASE

Nonerosive GERD (EGD negative)

Esophagitis

Barrett’s Metaplasia and Adenocarcinoma

Bleeding

Stricture

Extraesophageal GERD

Dental

Asthma

ENT

Impairs Quality of Life

EGD = esophagogastroduodenoscopy; ENT = ear, nose, and throat.
GERD SYMPTOM PROFILE ON PRESENTATION IN PRIMARY CARE

Heartburn in population

<table>
<thead>
<tr>
<th>Rank</th>
<th>Symptom</th>
<th>Estimated visits</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Abdominal pain</td>
<td>15,863,956</td>
</tr>
<tr>
<td>2</td>
<td>Diarrhea</td>
<td>4,236,051</td>
</tr>
<tr>
<td>3</td>
<td>Constipation</td>
<td>3,175,842</td>
</tr>
<tr>
<td>4</td>
<td>Vomiting</td>
<td>2,861,790</td>
</tr>
<tr>
<td>5</td>
<td>Nausea</td>
<td>2,814,364</td>
</tr>
<tr>
<td>6</td>
<td>Heartburn and indigestion</td>
<td>1,982,517</td>
</tr>
<tr>
<td>7</td>
<td>Rectal bleeding</td>
<td>1,702,331</td>
</tr>
<tr>
<td>8</td>
<td>Other GI symptoms, unspecified</td>
<td>1,357,602</td>
</tr>
<tr>
<td>9</td>
<td>Dysphagia</td>
<td>1,148,041</td>
</tr>
<tr>
<td>10</td>
<td>Gastrointestinal bleeding</td>
<td>1,073,771</td>
</tr>
<tr>
<td>11</td>
<td>Appetite decrease</td>
<td>725,705</td>
</tr>
<tr>
<td>12</td>
<td>Bloating and distention</td>
<td>699,928</td>
</tr>
<tr>
<td>13</td>
<td>Anorectal symptoms (including incontinence)</td>
<td>520,772</td>
</tr>
<tr>
<td>14</td>
<td>Symptoms related to the liver and biliary system</td>
<td>454,355</td>
</tr>
</tbody>
</table>

NOTE. Data are from 2009 National Ambulatory Medical Care Survey (http://www.cdc.gov/nchs/ahcd.htm).
Pathophysiology of GERD

- Impaired esophageal clearance
- Hiatal hernia
- Transient, inappropriate relaxations of LES
- Gastric acid; Pepsin secretion: normal/raised
- Pyloric incompetence; duodenogastric reflux
- Impaired salivary function
- Impaired esophageal mucosal defense
- Reduced resting pressure of LES
- Delayed gastric emptying
TRANSIENT LES RELAXATION (TLERS)

TLERS’s are induced by gastric distention and inhibited by GABA$_B$ receptors.
H. HERNIA AND GERD

Increased TLER’S’s are induced by:

• gastric distention
• impaired esophageal clearance
• reflux-acid and bile.
OBESITY AND GERD

Fig. 3 The dose–response association between abdominal diameter and the risk of GERD symptoms. Increased abdominal diameter (adjusted for BMI) was a consistent-independent risk factor for GERD-symptoms in whites (adopted from ref. [44])
OBESITY AND GERD

- Inflammation
- Tonus of EGJ
- Motility abnormalities
- Fibrogenesis
- Metaplasia (Barrett)
- Carcinogenesis

IL-6
TNF-α
IL-1β
Leptin
Adiponectin

H+ movement and regulation.
NON-EROSIVE REFLUX DISEASE

- Heartburn with normal appearing esophageal mucosa on endoscopy
- Most common form of GERD
- Less response to acid blockade vs erosive form of GERD
NERD VS GERD

- Endoscopy Negative: 70%
- Esophagitis: 30%
Mild Reflux: NERD

Moderate to Severe Reflux: Erosive Esophagitis

Severe Reflux: Barrett’s Esophagus

NERD = nonerosive reflux disease.

NON-EROSIVE REFUX DISEASE

Abnormal Reflux

- Acid mediated
- Non–acid mediated

No Reflux

- Functional
- Not uniquely chemosensitive
- Not uniquely mechanosensitive
ANTI-REFLUX TREATMENT

Lifestyle modifications

Medications

- Antacids
- H2-blockers
- Proton Pump Inhibitors (PPIs)

Anti-reflux surgery

Research question:

*How does refluxed acid induce such painful sensation?*
MECHANISM FOR HEARTBURN IN NERD

Stratified Squamous Epithelium

LUMINAL ACID

Brain

Spinal Cord

To Cortex

To Muscle

Reflex Arc

Nerve Plexus

Muscularis Propria

Barlow et al Gastroenterology 2005;171:771-78.
MAST CELL NERVE INTERACTIONS
Esophageal sensory nerves (A) (PGP9.5) are identified in proximity to mast cells (B) (tryptase) from human esophageal biopsy specimens.

Courtesy Dr. Yu Johns Hopkins
HEARTBURN SCORE AND ESOPHAGEAL MAST CELL DENSITY

\[ p < 0.03, n = 48 \]

Heartburn Score

![Bar graph showing heartburn score vs. esophageal mast cell density](image)

Esophageal Mast Cell Density (mm²)

Courtesy Dr. Yu Johns Hopkins
ACID ACTIVATESafferent 
AFTER ALLERGY

Acid (pH=2-3) → Action potentials

Acid (pH=2-3) → No response

Mast cell activation

Action potentials

Nodose

Vagal afferents

Courtesy Dr. Yu Johns Hopkins
NEUROTROPHIC MEDICATIONS (TCAS, SSRIS, ETC.) MAY BLOCK THE PAIN GATE
The role of the 5-hydroxytryptamine pathway in reflux-induced esophageal mucosal injury in rats

Lirong Yang1,2,3, Haifang Cai1,2,4, Jinfu Tou1,2, Weizhong Gu1,2, Xiaoli Shu1,2, Ting Zhang1,2, Xi Yang1,2, Zheng Shen1,2 and Mizu Jiang1,2*

Abstract

Background: Dysfunction of the 5-hydroxytryptamine (5-HT) signaling pathway can lead to gastrointestinal motility and secretion abnormalities and to visceral hypersensitivity. The aim of this study is to investigate the role of 5-HT in reflux-induced esophageal mucosal injury.

Methods: Fifty 8-week-old male Sprague-Dawley (SD) rats were randomly divided into a gastroesophageal reflux (GER) model group (30 rats) and a sham surgery control group (20 rats). Four weeks after surgery, the esophageal mucosa was collected for histological evaluation, 5-HT concentrations, and 5-HT selective reuptake transporter (SERT) mRNA and 5-HT4 receptor (5-HT4R) protein expressions.

Results: Twenty-seven rats in the GER model group survived, and three rats died. Histologically, in the GER model group, 20 rats had reflux esophagitis (RE group), and 7 rats had non-erosive reflux disease (NERD group). The 5-HT levels in the esophageal tissue from the RE group were significantly higher than those from the control and NERD groups. Both the RE and NERD groups showed significant increases in SERT mRNA expression of the esophageal mucosa than that of the controls, and the SERT mRNA level in the RE group was significantly higher than that in the NERD group.
GABA AND GERD

• Neurons w GABA receptors inhibit TLESRs
• Baclofen is a GABA$_B$ receptor agonist
• Frequent side effects
• Try GABA agonists
• Beta-Phenyl-gamma-aminobutyric acid – better BBB penetration
Three large cohort studies examining health issues in World Trade Center rescuers paint a mixed picture, with disturbingly high rates of physical and mental disorders but a paradoxically low all-cause mortality rate thus far, researchers reported in the Lancet.

More than 50,000 people participated in rescue and recovery work following the 2001 attacks on the World Trade Center.

A cohort study including 27,449 of those people who are enrolled in the federally funded WTC Screening, Monitoring, and Treatment Program showed a 9-year cumulative incidence of 28% for asthma, 42% for sinusitis, 39% for gastroesophageal reflux disease (GERD), and 43% for irritable bowel syndrome. Mortality in 28,593 bystanders – nonparticipants in the rescue and recovery work who lived or worked in lower Manhattan – was 39% lower than expected. Both reductions were significant.

Among rescue and recovery workers, higher levels of exposure to toxic dust and other WTC-related hazards were not significantly associated with higher risk of GERD or overall mortality. The New York City Department of Health and Mental Hygiene, and her associates (Lancet 2011;378:879-87).

Ongoing Monitoring Crucial
The investigators observed that the reduced mortality in the WTC-exposed population could be explained by a combination of bias due to the healthy worker effect and insufficiently long mortality is a must, the researchers added.

The studies were variously funded by the Centers for Disease Control and Prevention, the New York City Department of Health and Mental Hygiene, and the National Institute for Occupational Safety and Health. Dr. Wisnivesky is member of the research board of EHE International. All of the other investigators are co-authors of the other studies involved.

"Post 911 recovery workers have a 39% prevalence of GERD. Between 40-50% of post-911 recovery workers have persistent mental disorders such as anxiety, panic disorders, depression or PTSD. 70% of workers with a diagnosed mental disorder had GERD."
DIET AND LIFESTYLE MODIFICATION

- Dietary measures (avoidance):
  - Chocolate
  - Citrus fruits/fruit juices
  - Tomatoes
  - Peppermint
  - Onions/garlic
  - High-fat meals
  - Carbonation
- Small meal size

- Weight loss
- Smoking cessation
- Avoidance of alcohol (in particular white wine)
- Elevation of the head of the bed
- Sleeping in the left decubitus position
- No meals within 3 hours of sleeping

ALTERNATIVE THERAPIES FOR GERD

• Acupuncture
• Low carbohydrate diet
• **Melatonin**
• Chinese honeysuckle flower
• Liquid herbal formula with prokinetics e.g. Chelidonium
• DGL, slippery elm
• Aloe vera, zinc-l-carnosine (repair)
• GABA, beta-phenyl-gamma-aminobutyric acid
• Reduction of hiatal hernia; chiropractic, osteopathic, visceral manipulation
The potential therapeutic effect of melatonin in gastro-esophageal reflux disease

Tharwat S Kandil1*, Amany A Mousa2, Ahmed A El-Gendy3, Amr M Abbas3

Abstract

Background: Gastro-Esophageal Reflux Disease (GERD) defined as a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications. Many drugs are used for the treatment of GERD such as omeprazole (a proton pump inhibitor) which is a widely used antiulcer drug demonstrated to protect against esophageal mucosal injury. Melatonin has been found to protect the gastrointestinal mucosa from oxidative damage caused by reactive oxygen species in different experimental ulcer models. The aim of this study is to evaluate the role of exogenous melatonin in the treatment of reflux disease in humans either alone or in combination with omeprazole therapy.

Methods: 36 persons were divided into 4 groups (control subjects, patients with reflux disease treated with melatonin alone, omeprazole alone and a combination of melatonin and omeprazole for 4 and 8 weeks) Each group consisted of 9 persons. Persons were subjected to thorough history taking, clinical examination, and investigations including laboratory, endoscopic, record of esophageal motility, pH-metry, basal acid output and serum gastrin.

Results: Melatonin has a role in the improvement of Gastro-esophageal reflux disease when used alone or in combination with omeprazole. Meanwhile, omeprazole alone is better used in the treatment of GERD than melatonin alone.

Conclusion: The present study showed that oral melatonin is a promising therapeutic agent for the treatment of GERD. It is an effective line of treatment in relieving epigastric pain and heartburn. However, further studies are required to confirm the efficacy and long-term safety of melatonin before being recommended for routine clinical use.

Trial Registration: QA13NCT00915616
# EFFECTS OF MELATONIN ON PATIENTS WITH GERD

## GROUP II (N = 9)

<table>
<thead>
<tr>
<th>Symptoms:</th>
<th>Pretreatment with melatonin</th>
<th>4 weeks Post treatment with melatonin</th>
<th>8 weeks Post treatment with melatonin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Heart burn:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>7</td>
<td>3 (57.1%)</td>
<td>0 (100%)</td>
</tr>
<tr>
<td>Duration (months)</td>
<td>1.3 ± 0.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-Epigastric pain:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>6</td>
<td>3 (50%)</td>
<td>1 (83%)</td>
</tr>
<tr>
<td>Duration (months)</td>
<td>1.4 ± 0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B) LES Study:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-LES pressure (mmHg)</td>
<td>10 ± 1.58</td>
<td>14.5 ± 1.58</td>
<td>20.2 ± 1.56 ab</td>
</tr>
<tr>
<td>2-Residual pressure (mmHg)</td>
<td>0.012 ± 0.52</td>
<td>0.2 ± 0.016</td>
<td>0.32 ± 0.013ab</td>
</tr>
<tr>
<td>3-Relaxation duration (seconds)</td>
<td>6.8 ± 0.12</td>
<td>5.9 ± 0.16 a</td>
<td>5.3 ± 0.12 a</td>
</tr>
<tr>
<td>4-Relaxation %</td>
<td>86 ± 0.87</td>
<td>90 ± 0.86 a</td>
<td>100 ± 0.00 ab</td>
</tr>
<tr>
<td>C) PH (at 5 cm above the LES):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D) BAO (mmol/h)</td>
<td>24.7 ± 0.5</td>
<td>20.1 ± 0.4 a</td>
<td>16.6 ± 0.6 ab</td>
</tr>
<tr>
<td>E) Serum Gastrin (pg/ml)</td>
<td>22.1 ± 3.2</td>
<td>27.2 ± 23 a</td>
<td>32.3 ± 2.1 ab</td>
</tr>
<tr>
<td>D) Melatonin level at day time (pg/ml):</td>
<td>18.2 ± 5.54</td>
<td>28.26 ± 226 a</td>
<td>34.5 ± 235 ab</td>
</tr>
</tbody>
</table>

a: p < 0.05 relative to pretreatment with melatonin  
b: p < 0.05 relative to 4 weeks post treatment with melatonin
EFFECTS OF OMEPRAZOLE ON PATIENTS WITH GERD

GROUP III (N = 9)

<table>
<thead>
<tr>
<th></th>
<th>Pretreatment with omeprazole</th>
<th>4 weeks Post treatment with omeprazole</th>
<th>8 weeks Post treatment with omeprazole</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A) Symptoms:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-Heart burn:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>7</td>
<td>2 (71.4%)</td>
<td>0 (100%)</td>
</tr>
<tr>
<td>Duration (months)</td>
<td>1.2 ± 0.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-Epigastric pain:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>6</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Duration (months)</td>
<td>1.3 ± 0.4</td>
<td>(66.7%)</td>
<td>(100%)</td>
</tr>
<tr>
<td><strong>B) LES Study:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-LES pressure (mmHg)</td>
<td>10.5 ± 2.86</td>
<td>10.4 ± 4.05</td>
<td>10.5 ± 2.85</td>
</tr>
<tr>
<td>2-Residual pressure (mmHg)</td>
<td>0.1 ± 0.064</td>
<td>0.2 ± 0.15</td>
<td>0.1 ± 0.07</td>
</tr>
<tr>
<td>3-Relaxation duration (seconds)</td>
<td>6.5 ± 2.74</td>
<td>6.3 ± 2.7</td>
<td>6.3 ± 2.65</td>
</tr>
<tr>
<td>4-Relaxation %</td>
<td>87.2 ± 0.17</td>
<td>87.3 ± 0.25</td>
<td>87.1 ± 0.1</td>
</tr>
<tr>
<td>C) PH (at 5 cm above the LES):</td>
<td>2.1 ± 0.38</td>
<td>5.9 ± 0.48a</td>
<td>7.2 ± 0.32ab</td>
</tr>
<tr>
<td>D) BAO (mmol/h)</td>
<td>25.1 ± 0.6</td>
<td>17.2 ± 0.7a</td>
<td>11.5 ± 0.6ab</td>
</tr>
<tr>
<td>E) Serum Gastrin (pg/ml)</td>
<td>21.5 ± 4.6</td>
<td>32.1 ± 2.1a</td>
<td>35.9 ± 1.8ab</td>
</tr>
<tr>
<td>D) Melatonin level at day time (pg/ml):</td>
<td>18.5 ± 3.75</td>
<td>19.2 ± 3.47</td>
<td>17.9 ± 3.72</td>
</tr>
</tbody>
</table>

a: p < 0.05 relative to pretreatment with melatonin
b: p < 0.05 relative to 4 weeks Post treatment with melatonin

BMC Gastroenterology 2010, 10:7
EFFECTS OF MELATONIN AND OMEPRAZOLE ON PATIENTS WITH GERD GROUP IV (N = 9)

<table>
<thead>
<tr>
<th></th>
<th>Pretreatment with melatonin and omeprazole</th>
<th>4 weeks Post treatment with melatonin and omeprazole</th>
<th>Post 8 weeks treatment with melatonin and omeprazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>A) Symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-Heart burn:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>8</td>
<td>1 (87.5%)</td>
<td>0 (100%)</td>
</tr>
<tr>
<td>Duration (months)</td>
<td>1.4 ± 0.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-Epigastric pain:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>6</td>
<td>1 (83.3%)</td>
<td>0 (100%)</td>
</tr>
<tr>
<td>Duration (months)</td>
<td>1.3 ± 0.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B) LES Study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-LES pressure (mmHg)</td>
<td>10.3 ± 1.68</td>
<td>14.5 ± 1.26a</td>
<td>20.5 ± 1.22ab</td>
</tr>
<tr>
<td>2-Residual pressure (mmHg)</td>
<td>0.012 ± 0.44</td>
<td>0.21 ± 0.016</td>
<td>0.33 ± 0.016a</td>
</tr>
<tr>
<td>3-Relaxation duration (seconds)</td>
<td>6.8 ± 0.16</td>
<td>5.8 ± 0.13a</td>
<td>5.2 ± 0.12a</td>
</tr>
<tr>
<td>4-Relaxation %</td>
<td>85 ± 1.58</td>
<td>90 ± 1.23a</td>
<td>100 ± 0.00ab</td>
</tr>
<tr>
<td>C) PH (at 5 cm above the LES)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D) BAO (mmol/h)</td>
<td>24.9 ± 0.7</td>
<td>15.8 ± 0.9a</td>
<td>10.2 ± 0.9ab</td>
</tr>
<tr>
<td>E) Serum Gastrin (pg/ml)</td>
<td>21.9 ± 4.7</td>
<td>33.6 ± 2.7a</td>
<td>368 ± 2.1ab</td>
</tr>
<tr>
<td>D) Melatonin level at day time (pg/ml):</td>
<td></td>
<td>18.3 ± 3.8</td>
<td>28.83 ± 1.82ab</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>34.5 ± 2.35ab</td>
</tr>
</tbody>
</table>

a: p < 0.05 relative to pretreatment with melatonin
b: p < 0.05 relative to 4 weeks Post treatment with melatonin
ALTERNATIVE THERAPIES FOR GERD

• Raft forming agents
  – alginate, pectin, carbenoxolone
• Anti-anxiety
  – D-limonene
• Anti-oxidants
  Artemisia asiatica
  Curcumin
  Quercetin
  Vitamin E
ACID POCKET

- This acid pocket extends from the cardia, across the GEJ, into the distal esophagus
- Can extend 6 cm above the diaphragmatic pinch
- Length of acid pocket correlated with scintigraphy images (p<.0001)

ACID POCKET: HIATAL HERNIA

*Transient Lower Esophageal Sphincter Relaxations*

ALGINATE

Anionic polysaccharide found in cell walls of brown algae

ALGINATE ANTACIDS

Alginate
+
Sodium or Potassium Bicarbonate
+
Antacid

ALGINATE ANTACIDS

• Alginate precipitates in gastric acid, forming a gel
• Bicarbonate converts to CO2 which becomes trapped in the gel
• This results in a relatively pH-neutral floating barrier

ALIMENTARY TRACT

An Alginate-Antacid Formulation Localizes to the Acid Pocket to Reduce Acid Reflux in Patients With Gastroesophageal Reflux Disease

WOUT O. ROHOF,* ROEL J. BENINK,‡ ANDRE J. P. M. SMOOUT,* EDWARD THOMAS,§ and GUY E. BOECKXSTAENS‖

*Department of Gastroenterology and Hepatology, and ‡Department of Nuclear Medicine, Academic Medical Centre, Amsterdam, the Netherlands; §Reckitt Benckiser, Slough, Berkshire, United Kingdom; and ‖Translational Research Center for Gastrointestinal Disorders (TARGID), University of Leuven, Leuven, Belgium
ALGINATE ANTACIDS

- **Alginate** precipitates in gastric acid, forming a gel
- **Bicarbonate** converts to CO2 which becomes trapped in the gel
- This results in a relatively pH-neutral floating barrier

METHODS: INCLUSION CRITERIA

• Adult patients with GERD as defined as
  – Typical GERD symptoms AND
  – Esophagitis on EGD AND/OR
  – 24-hour pH study with pH <4 with >4.5% exposure time

• Patients MUST have hiatal hernia >3 cm
METHODS

GERD patients
n = 16

10 mL Antagel
n = 8

10 mL Gaviscon DA
n = 8

Antagel Mg hydroxide
and Al oxide
RESULTS: LOCALISATION

A: Acid pocket
B: Alginate raft
C: Superimposed
RESULTS: REFLUX

A

Reflux episodes

Nr of reflux episodes

Antacid

Gaviscon

P = .05

B

Acid reflux episodes

Nr of reflux episodes

Antacid

Gaviscon

P = .03

Clinical Gastroenterology and Hepatology 2013; 11:1585-1591
(DOI:10.1016/j.cgh.2013.04.046)

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RESULTS: REFLUX

A. pH > 4 in acid pocket

B. Time to acid reflux

C. Mean pH of reflux episodes

Clinical Gastroenterology and Hepatology 2013; 11:1585-1591
(DOI:10.1016/j.cgh.2013.04.046)

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STUDY IMPORTANCE/RELEVANCE

• Consider Gaviscon alone over antacid for episodic postprandial heartburn
• Role in treatment of patients with large HH
• Offers a non-systemic treatment of GERD (ie. pregnancy, comorbidities)
Table 6. Product active ingredients and ANCs.

<table>
<thead>
<tr>
<th>Product</th>
<th>Active ingredients listed (mg per maximum dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gaviscon Double Action Liquid</td>
<td>Sodium alginate (1000)</td>
</tr>
<tr>
<td></td>
<td>Sodium bicarbonate (426)</td>
</tr>
<tr>
<td></td>
<td>Calcium carbonate (650)</td>
</tr>
<tr>
<td>Gaviscon Liquid</td>
<td>Sodium alginate (1000)</td>
</tr>
<tr>
<td></td>
<td>Sodium bicarbonate (534)</td>
</tr>
<tr>
<td></td>
<td>Calcium carbonate (320)</td>
</tr>
<tr>
<td>Gastrocote</td>
<td>Sodium alginate (660)</td>
</tr>
<tr>
<td></td>
<td>Dried aluminium hydroxide (240)</td>
</tr>
<tr>
<td></td>
<td>Sodium bicarbonate (210)</td>
</tr>
<tr>
<td></td>
<td>Magnesium trisilicate (120)</td>
</tr>
<tr>
<td>Gaviscon Regular Strength (USA)</td>
<td>Magnesium carbonate (716)</td>
</tr>
<tr>
<td></td>
<td>Aluminium hydroxide (190)</td>
</tr>
<tr>
<td>Gaviscon Extra Strength (USA)</td>
<td>Aluminium hydroxide (1016)</td>
</tr>
<tr>
<td></td>
<td>Magnesium carbonate (950)</td>
</tr>
<tr>
<td>Mylanta Heartburn Relief</td>
<td>Calcium carbonate (500)</td>
</tr>
<tr>
<td></td>
<td>Sodium bicarbonate (500)</td>
</tr>
<tr>
<td></td>
<td>Dried aluminium hydroxide (400)</td>
</tr>
<tr>
<td></td>
<td>Magnesium hydroxide (400)</td>
</tr>
<tr>
<td></td>
<td>Alginic acid (310)</td>
</tr>
<tr>
<td>Rennie Liquid Relief</td>
<td>Calcium carbonate (1200)</td>
</tr>
<tr>
<td></td>
<td>Sodium alginate (300)</td>
</tr>
<tr>
<td></td>
<td>Magnesium carbonate (140)</td>
</tr>
</tbody>
</table>

- Quantities of active ingredients vary greatly
- *In vitro* testing on raft formation

TRANSIT TIME MODULATORS

• Ginger 1,500 mg per day
• Liquid digestive herbal formula 20 drops 2-3x/day
• Acupuncture 3x per week
• D-limonene 1,000 mg BID
• Probiotics-variable dosing
• Chinese herbs (TJ 43)
POTENTIAL RISKS OF PPIs

• Increased risk of infection
  – Bacterial overgrowth
  – C. difficile
  – Gastroenteritisides
    (salmonella, campylobacter)
  – Pneumonia

• Malabsorption
  – Calcium, Mg, Iron
  – Vitamin B12

• Osteoporosis

• Plavix interference

Williams C. Aliment Pharmacol Ther. 2006;23:3-10.
Figure Legend:
Association between a 2 or more years’ supply of proton pump inhibitors (PPIs) and a diagnosis of vitamin B₁₂ deficiency, stratified by time since most recent prescription. Patients in the current user category received their last PPI prescription in the last year prior to the index date; those in the recent user category received their last PPI prescription 1 to 1.9 years prior to the index date; those in the former user category received their last PPI prescription 2 to 2.9 years prior to the index date; those in the remote former user category received their last PPI prescription 3 or more years prior to the index date.
INFECTIOUS RISK: C. difficile

- 90% of patients with C. diff have had antibiotic exposure within 8 weeks
- Large meta-analysis reviewed 313,000 participants in 39 studies and showed statistically significant association between PPI use and risk of developing CDI

**POOLED RISK PPIS C. *difficle***

![Risk of *Clostridium difficile* recurrence with proton-pump inhibitor (PPI) use.](image)

Figure 3. Risk of *Clostridium difficile* recurrence with proton-pump inhibitor (PPI) use.

SMALL BOWEL BACTERIAL OVERGROWTH

• Systematic review and meta-analysis of 11 studies encompassing 3134 patients were using PPI to determine risk of SIBO.

• PPI use statistically was associated with SIBO risk, but only when the diagnosis was made by a highly accurate test (duodenal or jejunal aspirate culture).

CARDIOVASCULAR RISK: HOW

- PPIs are metabolised by the cytochrome P450 pathway, specifically CYP2C19 and CYP3A4.
- As a prodrug, clopidogrel requires a biotransformation to be converted into its active form, a process also mediated by the CYP2C19 and CYP3A4 enzymes.
- This reliance on the same pathway has led to the hypothesis that competition at CYP2C19 may reduce the biological activity of clopidogrel.
- Omeprazole and esomeprazole more highly indicted than other agents due to their CYP activity
D’UGO ET AL. PROTON PUMP INHIBITORS AND CLOPIDOGREL, AN ASSOCIATION TO AVOID? INTERN EMERG MED JULY 2013

The diagram illustrates the metabolism of clopidogrel and its active metabolite (R = 130964) by various CYP enzymes. The active metabolite is further metabolized to a non-enzymatic pathway. The CYP enzymes involved include CYP2C19, CYP3A4, CYP2B6, CYP2C9, and CYP1A2.
UNEXPECTED EFFECT OF PROTON PUMP INHIBITORS: CLINICAL PERSPECTIVE

“PPIs are widely used for gastroesophageal disease (GERD). Whereas their short term use appears to be safe, these drugs were never approved for long-term use.”

“Patients that require long-term suppression of gastric acidity might be switched to H2-receptor antagonists like ranitidine, which does not have the adverse effect on the vasculature described in our report.”

“These individuals may be a greater risk for cardiovascular disease. Patients should discuss with their doctors the risks of long-term PPI use, which include low magnesium levels, tendency for irregular heartbeats, and an increased risk of bone fractures. Our new data adds another potential risk of long-term use.”

John P. Cooke, MD, PhD, Professor and Chair, Department of Cardiovascular Sciences, Texas Methodist Research Institute
INTERSTITIAL NEPHRITIS

• Patients typically present with symptoms of renal failure, (nausea, vomiting and fatigue).
• Injury to the medulla can inhibit the ability to concentrate urine, (polyuria and polydipsia).
• May have acute elevation in Cr levels, maculopapular rash, proteinuria, pyuria (in almost all cases), hematuria (in 90% of cases), and eosinophiluria (in 80% of cases).
• Timely diagnosis is important because early intervention (withdrawal of PPI promptly in the first week) improves the outcome.


Chang Y, Hypersensitivity reactions to proton pump inhibitors Current Opinion in Allergy & Clinical Immunology. 12(4):348-353, August 2012.
From Medscape Medical News

Watchdog Group Seeks 'Black Box' Warning on PPIs
Megan Brooks

August 24, 2011 — The nonprofit consumer advocacy group Public Citizen is petitioning the US Food and Drug Administration (FDA) to add black box warnings to the product labels of all proton pump inhibitors (PPIs) on the market.

The black box warnings should alert clinicians and patients that these drugs can cause long-term dependence and other serious adverse effects, Public Citizen says in a statement released yesterday.

The group is also calling for patient medication guides to be distributed with all PPIs and for the makers of the drugs to notify clinicians of these adverse effects and of the need to try safer alternatives first for conditions such as gastroesophageal reflux disease (GERD).

"These drugs are being prescribed far too commonly to people who shouldn't be taking them," Sidney Wolfe, MD, director of Public Citizen's Health Research Group, said in a prepared statement. "As a result, millions of people are needlessly setting themselves up to become dependent on PPIs while exposing themselves to the serious risks associated with long-term therapy.

"The FDA should act immediately to ensure that patients and physicians are adequately warned of these effects, and reminded of the many safer alternatives for common conditions such as acid reflux," he added.

More Education, Not Warnings, Needed

Reached for independent comment, Kenneth DeVault, MD, professor and chair, Department of Medicine, Mayo Clinic, Jacksonville, Florida, told Medscape Medical News that he does not think that greater warnings are needed on PPIs. "But that education of providers and consumers is important."
FDA WARNING: MAGNESIUM

As of 2/2012 FDA informs the public that:

• PPI may rarely cause low serum magnesium levels if taken for prolonged periods of time (in most cases, longer than one year).

• In approximately one-quarter of the cases reviewed, magnesium supplementation alone did not improve low serum magnesium levels and the PPI had to be discontinued.

• Recommendation:
  – check magnesium level in those on long-term PPI therapy
  – ensure that there is an indication for long-term therapy

BONE FRACTURE

• Several reports linking bone fractures and osteoporosis to PPI use
• Recent review (biased?) concluded that there is no good evidence to establish that PPI use has a significant risk for bone density loss or osteoporotic-related fractures.
• Follow the evidence—caution elderly and post-menopausal women and others.

Johnson et al. Reported side effects and complications of long-term proton pump inhibitor use: dissecting the evidence clin gastro and hep 2013 corrected proof on-line.
Perspectives in Clinical Gastroenterology and Hepatology

Reported Side Effects and Complications of Long-term Proton Pump Inhibitor Use: Dissecting the Evidence

DAVID A. JOHNSON and EDWARD C. OLDFIELD IV

Gastroenterology Division, Department of Medicine, Eastern

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BONE FRACTURE

New study show possible aetiology

- In a study of 1038 community dwelling older persons, chronic use of PPI was negatively associated with bone mineral density measured by CT.
- The FDA issued warnings regarding the potential for wrist, hip, and spine fractures among PPI users in 2010.

Maggio et al. Use of proton pump inhibitors is associated with lower trabecular bone density in older individuals. Bone 57 (2013) 437-442.
### SUMMARY OF THE EVIDENCE

**Table 1. Epidemiologic evidence supporting an association between proton pump inhibitors and adverse effects**

<table>
<thead>
<tr>
<th>Potential PPI adverse effects</th>
<th>Assessment criteria</th>
<th>Consistency of association</th>
<th>Biologically plausible mechanism</th>
<th>Supportive experimental evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>B12 deficiency</td>
<td>Low magnitude (Ratio &lt;2)</td>
<td>Inconsistent</td>
<td>Interaction biologically plausible</td>
<td>Failed to demonstrate an association</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>Low magnitude (Ratio &lt;2)</td>
<td>Inconsistent</td>
<td>Interaction biologically plausible</td>
<td>Failed to demonstrate an association</td>
</tr>
<tr>
<td>Rebound acid hypersecretion</td>
<td>Low magnitude (Ratio &lt;2)</td>
<td>Inconsistent</td>
<td>Interaction biologically plausible</td>
<td>Failed to demonstrate an association</td>
</tr>
<tr>
<td>Acute interstitial nephritis</td>
<td>Low magnitude (Ratio &lt;2)</td>
<td>Inconsistent</td>
<td>Interaction biologically plausible</td>
<td>Failed to demonstrate association</td>
</tr>
<tr>
<td>Gastric carcinoid tumor</td>
<td>Low magnitude (Ratio &lt;2)</td>
<td>Inconsistent</td>
<td>Interaction biologically plausible</td>
<td>Failed to demonstrate an association</td>
</tr>
<tr>
<td>Cardiovascular risk (clopidogrel interaction)</td>
<td>Low magnitude (Ratio &lt;2)</td>
<td>Inconsistent</td>
<td>Interaction biologically plausible</td>
<td>Failed to demonstrate an association</td>
</tr>
<tr>
<td>Bone fractures</td>
<td>Low magnitude (Ratio &lt;2)</td>
<td>Inconsistent</td>
<td>Interaction biologically plausible</td>
<td>Mixed results</td>
</tr>
<tr>
<td>Enteric infections</td>
<td>Higher magnitude (Ratio &gt;2)</td>
<td>Inconsistent</td>
<td>Interaction biologically plausible</td>
<td>Mixed results</td>
</tr>
<tr>
<td>Respiratory infections</td>
<td>Low magnitude (Ratio &lt;2)</td>
<td>Inconsistent</td>
<td>Interaction biologically plausible</td>
<td>Failed to demonstrate an association</td>
</tr>
</tbody>
</table>

PPI, proton pump inhibitor.

Abraham, Current Opinion
Gastro 2012 (28)615-620.
As a consequence, a substantial proportion, if not majority, of patients now prescribed proton-pump inhibitor therapy do not have acid-related symptoms and therefore have no true indication for such therapy.

The current finding that these drugs induce symptoms means that such liberal prescribing is likely to be creating the disease the drugs are designed to treat and causing patients with no previous need for such therapy to require intermittent or long-term treatment.

Gastroenterology. June 2009
It is likely also that treatment of mild reflux symptoms with such therapy may aggravate the underlying disease and lead to an increased requirement for long-term therapy.

Studies are required to investigate whether early treatment of mild reflux disease with proton-pump inhibitor therapy results in aggravation of the natural history of the condition.
"You’re not ill yet, Mr. Blendell, but you’ve got potential - so I am going to prescribe a PPI."
PPI WEANING

Factors to consider

- Gastrin (>300 pg/mL)
- Duration of use (>5 yrs)
- Frequency of PPI use (BID)
- Hiatal hernia (> 3 cm)
- Gastroparesis
- Barrett’s esophagus
- LA grade B or higher disease
- Uncontrolled stress
PPI WEANING

Game plan for weaning

• Always should be done under supervision
• Never cold turkey a PPI!
• Correct underlying pathophysiology while maintaining acid-suppression (gastroparesis, stress, etc.) and adding supplements (alginate, DGL, Zn carnosine etc.)
• Alternate day PPI while adding gentle form of acid suppression: e.g. H2 blocker or melatonin
• Maintenance gentle acid suppression
• Switch to OTC PRN
PPI Weaning

Patient with GERD on PPI w rebound on withdrawal

Lifestyle modifications, stress reduction, fix H hernia, address motility, supplements, GFD, gradual taper

Response

No Response

Has a different condition

pH Monitoring, EGD, biopsy to rule out Eosinophilic Esophagitis
GERD Algorithm

Patient with heartburn, regurgitation, anxiety/stress?

YES

Stress/anxiety modulation

Continue

no response

NO

Lifestyle modification, supplements

Hiatal hernia Motility Disorder

EGD, pH monitoring; GERD vs NERD