Optimal Management of GERD with Dexlansoprazole
- Extended plasma concentration and dosing flexibility with a dual delayed release PPI

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## Prevalence of GERD in Korea
- *a population-based study in Asan-si*

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heartburn</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least monthly</td>
<td>4.8</td>
<td>4.6</td>
<td>4.7</td>
</tr>
<tr>
<td>At least weekly</td>
<td>1.9</td>
<td>2.1</td>
<td>2.0</td>
</tr>
<tr>
<td><strong>Acid regurgitation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least monthly</td>
<td>3.8</td>
<td>5.1</td>
<td>4.4</td>
</tr>
<tr>
<td>At least weekly</td>
<td>1.9</td>
<td>2.2</td>
<td>2.0</td>
</tr>
<tr>
<td><strong>Heartburn and/or</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>acid regurgitation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least monthly</td>
<td>7.6</td>
<td>8.9</td>
<td>8.2</td>
</tr>
<tr>
<td>At least weekly</td>
<td>3.5</td>
<td>3.5</td>
<td>3.5</td>
</tr>
</tbody>
</table>

CHO YS, Choi MG. Am J Gastroenterol 2005;100:747-753
Prevalence of GERD in health checkup

- Erosive esophagitis: 7%
- Reflux symptoms: 7%
- 3% overlap
- Total: 83%
### Average physiological pHs in GI tract

<table>
<thead>
<tr>
<th>Site</th>
<th>fasted</th>
<th>fed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach</td>
<td>1.4 - 2.1</td>
<td>3.0 - 7.0</td>
</tr>
<tr>
<td>Duodenum</td>
<td>4.9 - 6.4</td>
<td>5.1 - 5.2</td>
</tr>
<tr>
<td>Jejunum</td>
<td>4.4 - 6.5</td>
<td>5.2 - 6.2</td>
</tr>
<tr>
<td>Ileum</td>
<td>6.5 - 8.0</td>
<td>6.8 - 8.0</td>
</tr>
</tbody>
</table>

#### History of gastric acid & PPI

<table>
<thead>
<tr>
<th>Year</th>
<th>Person</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1823</td>
<td>Prout W</td>
<td>Discovery of gastric acid</td>
</tr>
<tr>
<td>1836</td>
<td>Schwann</td>
<td>Discovery of pepsin</td>
</tr>
<tr>
<td>1938</td>
<td>Komarov SA</td>
<td>Discovery of gastrin</td>
</tr>
<tr>
<td>1972</td>
<td>Black JW</td>
<td>Development of H2RA</td>
</tr>
<tr>
<td>1979</td>
<td>Olbe</td>
<td>Development of PPI</td>
</tr>
</tbody>
</table>
There are many “–zoles”.

- Omeprazole
- Lansoprazole
- Rabeprazole
- Pantoprazole
- Esomeprazole
- Illaprazole
A big exception: **Aripiprazole** (Abilify)

- an new antipsychotic—a dopamine system stabilizer
Today’s topic is about a relatively new member of the PPI family

- Omeprazole
- Lansoprazole
- Rabeprazole
- Pantoprazole
- Esomeprazole
- Illaprazole

- **Dexlansoprazole (Dexilant)**
Lansoprazole is a racemic mixture of R- and S-entantiomers.

Dexlansoprazole is the R-enantiomer of lansoprazole.

The R-enantiomer has a slower clearance rate and correspondingly higher circulating plasma concentrations than the S-enantiomer.
Dual Release Technology
- Dual Delayed Release (DDR) Formulation

 Dexilant capsules contain 2 types of granules

 Granule 1 begins releasing drug within an hour of dosing
 Granule 2 provides a second release of drug several hours later

Figure 2. Dexilant features a Dual Delayed Release (DDR) formulation, which contains 2 types of enteric-coated granules. Artistic rendition of granules.

The 2 types of enteric-coated Dexilant granules

Granule 1
- pH ≥5.5
- Sugar sphere
- Active-coating layer
- Middle (protective) layer
- Enteric coating layer 1

Granule 2
- pH ≥6.75
- Enteric coating layer 2

Figure 3. The 2 types of granules in each Dexilant capsule release medication at different pH levels in the GI tract.
Do you think our patients are happy enough?

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Patients are not satisfied as much as doctors.

The proportion of very satisfied or well controlled is higher by doctors’ assessment (blue bar) than the patients’ assessment (green bar).
GASTROENTEROLOGY

Unmet treatment needs of peptic ulcer disease in Asia: Gastroesophageal Reflux Disease Asia Pacific Survey

Khean Lee Goh,* Myung Gyu Choi,† William F. Qi,‡ Udom Kachintorn,§ Somchai Leelakusolvong,¶ Benjamin CY Wong, §§ Justin Wu, §§§ Cheng Tang, §§§§ Joseph C Bocobo, §§§§ Melchor M Chan §§§§§ and Jack K. P. Lee†††

Currently taking PPIs

Middle to upper income group

20-min face-to-face interview and full survey

Survey questions based on five key areas

Korea (n=80) Taiwan (n=80) Indonesia (n=80) Philippines (n=80) Thailand (n=80) Hong Kong (n=50)

450 patients
# Response to PPI therapy

<table>
<thead>
<tr>
<th>Treatment effect</th>
<th>Response number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eliminate pain</td>
<td>324 (72)</td>
</tr>
<tr>
<td>Take effect within 30 min</td>
<td>343 (76)</td>
</tr>
<tr>
<td>Sustain relief of discomfort</td>
<td>327 (73)</td>
</tr>
<tr>
<td>Provide nocturnal relief</td>
<td>346 (77)</td>
</tr>
<tr>
<td>Limited improvement in nocturnal relief</td>
<td>202 (45)</td>
</tr>
<tr>
<td>Take adjunctive therapy</td>
<td>221 (49)</td>
</tr>
<tr>
<td>Negative impact of symptoms on well being</td>
<td>343 (76)</td>
</tr>
</tbody>
</table>
Ideal GERD medication - Asian patients perspective

![Graph showing the percent of respondents who prioritize different aspects of GERD medication]

- Long term safety: 60%
- Eliminate nocturnal symptoms: 60%
- Enjoy daily activities: 50%
- Worry free: 50%
- Eliminate pain completely: 40%
- Reduce pain for 24 h: 40%
- Reduce pain quickly: 30%
- Eat/drink normally: 30%
- No dosing restrictions: 20%

Areas of unmet needs
- Dexilant is very useful for these areas.

• Night-time heartburn
• PPIs-dependence on food for efficacy
• Individual variation
• Advanced grades of erosive esophagitis
• Non-erosive reflux disease
1. Management of night-time symptoms or breakthrough symptoms with Dexlilant
Breakthrough symptom is not uncommon

Patient-Reported Symptoms on Once-Daily PPI Therapy (N=1064)

38% Breakthrough Symptoms

62% No Breakthrough Symptoms

Most Patients with breakthrough symptoms experience them at night

- At night: 65%
- While sleeping: 28%
- During the day: 45%
- In the morning: 16%

Adapted from American Gastroenterological Association. GERD Patient Study: Patients and Their Medications. Harris Interactive Inc; 2008. Available at www.sciencedaily.com/releases/2008/05/080515145404.htm Accessed Apr 9, 2018
Reasons for Increasing to Twice-Daily Dosing of a PPI

- **73.4%** Symptoms not controlled
- **39.1%** Symptoms not controlled at night
- **9.4%** Insurance coverage change
- **7.8%** Other

Percentage of respondents receiving twice-daily dosing
PPIs bind to active pumps only

Unstimulated proton pumps in cytoplasmic tubules

Inactive Parietal Cell

Gastrin

ACh

H₂
Most PPIs have short half-life

Proton pumps activated in this period are not blocked by PPI
Dual Release Technology
- Dual Delayed Release (DDR) Formulation

**Figure 2.** DEXILANT features a Dual Delayed Release (DDR) formulation, which contains 2 types of enteric-coated granules.\(^1\)

Figure 3. The 2 types of granules in each DEXILANT capsule release medication at different pH levels in the GI tract.\(^1,2\)
The DDR formulation results in a plasma concentration–time profile with two distinct peaks

- Granule 1 comprises 25% of total dose and is released at pH 5.5 within 2 hours of dosing
- Granule 2 comprises 75% of total dose and is released at pH 6.75 several hours after dosing
**DEXILANT® vs. Conventional Single Release PPI: Maintenance of Drug Concentration**

- **Drug concentration (ng/mL)**
  - Conventional PPI
  - DEXILANT® 30 mg
  - DEXILANT® 60 mg

- **Time (hours)**: 0, 4, 8, 12, 16, 20, 24
  - DEXILANT® 60 mg peaks at 125 ng/mL.

Vakily Curr Med Res Opin. 2009;25:627
DEXILANT® vs. Esomeprazole
after oral single dose

Mean plasma concentration-time curves

Mean intragastric pH

DEXILANT®: Effects on Sleep

- Nights with GERD-related Sleep disturbances
- Nights with Difficulty falling asleep
- Nights with waking
- Nights with Difficulty getting back to sleep
- Morning waking too early
- Morning waking up feeling tired
- Nights with sleep disturbances due to other reasons

Median percentage:

- Dexlansoprazole MR 30mg
- Placebo
Nights without GERD symptoms by Dexilants

24hr heartburn free day

- Placebo
- Dexlansoprazole 60mg

Nights without heartburn

- Placebo
- Dexlansoprazole 60mg

Howden CW. Aliment Pharmacol Ther 2009;30:895
2. Dexilant can be taken after the meal

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Sub-optimal PPI dosing in 54%

- 30-60 min before meals: 17%
- 15-30 min before meals: 26%
- <15 min before meals: 57%

- Optimal Dosing: 46%
- Sub-optimal Dosing: 54%

- As needed: 4%
- At bedtime: 28%
- >60 min before meals: 38%
- After meals: 30%

54% of patients dosed proton pump inhibitors sub-optimally

Gunaratnam NT. Aliment Pharmacol Ther. 2006;23;1473-7
Mean intragastric pH on day 3 while on Daxilant

3. Less influenced by CYP2C19 polymorphism
Dexilant was not significantly influenced by CYP2C19 polymorphism in Cmax

Mean±SD plasma concentration–time profiles of (R)-lansoprazole after a 60 mg oral dose of racemic lansoprazole for homozygous extensive metabolizers (EMs) (solid circles), heterozygous EMs (open circles), and poor metabolizers (PMs) (solid squares).
Dexlansoprazole and lansoprazole had no significant effect on the PD and antiplatelet activity of clopidigrel, while esomeprazole and omeprazole did.

IPA = inhibition of platelet aggregation; PRI = platelet reactivity index.

**Graph:**
- **% decrease in IPA**
  - Dexlansoprazole 60mg: -0.2%
  - Lansoprazole 30mg: -7.2%
  - Lansoprazole 30mg: -19.2%
  - Lansoprazole 30mg: -22.5%
- **% decrease in inhibition of PRI**
  - Dexlansoprazole 60mg: -2.5%
  - Lansoprazole 30mg: -27.1%
  - Lansoprazole 30mg: -35.2%
Dexilant – a strong long-acting PPI with dual delayed release (DDR) technology

1. Excellent control of breakthrough symptoms including night-time heartburn
2. Can be taken after the meal
3. Less individual variation