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PHAST PHACT

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TODAY'S TOPIC:

Refractory Acid Reflux
Options for Treatment

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If you have a topic you would like the pharmacy team to answer, please send your suggestions to: pruskowskija@upmc.edu

Background:

Approximately 10-40% of patients with gastroesophageal reflux disease (GERD) (i.e. acid reflux) fail to respond symptomatically, either partially or completely, to proton pump inhibitors (PPIs). Most patients with GERD who do not respond to a PPI have either nonerosive reflux (NERD) or functional heartburn. Below are the maximum daily doses of PPIs for acid reflux:

PPI	Maximum Daily Dose
Omeprazole	60mg/day
Pantoprazole	80mg/day
Lansoprazole	60mg/day

Of course, before considering other agents, consider using these maximum daily doses, appropriate administration and the metabolism of the PPI. PPIs should be administered 30 to 60 minutes before breakfast for maximal inhibition of proton pumps. In one study that included 100 patients with GERD, only 46% of patients prescribed a PPI for GERD were taking it as advised [Ref]. To add, PPIs are metabolized through the hepatic cytochrome system, with CYP2C19 having the dominant role. The activity of CYP2C19 is determined to some extent by a genetic polymorphism. Approximately 5 percent of Caucasian patients and >10 percent of Asians, are homozygous for a CYP2C19 mutation (i.e., slow metabolizers), potentially leading to greater suppression of gastric acidity. However, in wild type homozygotes (rapid metabolizers) the effect of PPIs on gastric acidity is diminished and may contribute to PPI failure.

Importance:

Refractory GERD can occur in many older adults and patients with serious illness, especially as often there are no reversible causes. Palliative care provides should be aware of the other options available for these patients to reduce symptom burden.

The Literature:

Option #1: Adding a bedtime H2RA (e.g. ranitidine):

- Gastroenterology. 1998 Dec;115(6):1335-9.

Ranitidine controls nocturnal gastric acid breakthrough on omeprazole: a controlled study in normal subjects.

- Methods: Twelve volunteers underwent overnight intragastric pH monitoring after 7 days of treatment with omeprazole, 20 mg twice daily, followed by different treatment supplements at bedtime: placebo; additional omeprazole, 20 mg; ranitidine, 150 mg; and ranitidine, 300 mg.
- Results: Additional omeprazole at bedtime reduced the percentage of time with intragastric pH of <4 from 48% to 31% ($P < 0.005$) compared with omeprazole twice daily with placebo at bedtime. Ranitidine at bedtime reduced this parameter more, 5% with 150 mg and 6% with 300 mg ($P < 0.01$ vs. omeprazole twice daily plus bedtime).
- Conclusion: "Bedtime ranitidine is more effective than bedtime omeprazole on residual nocturnal acid secretion in patients receiving omeprazole twice daily. This finding suggests that fasting breakthrough nocturnal acid secretion in patients receiving omeprazole twice daily is most likely histamine related"

Option #2: Adding a reflux inhibitor: baclofen

- Gastroenterol Res Pract. 2014;2014:307805.

  The effects of baclofen for the treatment of gastroesophageal reflux disease: a meta-analysis of randomized controlled trials.
  - Results: Nine studies were identified with a total of 283 GERD patients and healthy subjects. Comparative analysis provided high quality data supporting the ability of baclofen to promote a short-term decrease in the number of reflux episodes per patient, the average length of reflux episodes, and the incidence of transient lower esophageal sphincter relaxation. No serious adverse events or death events were reported, and there were no significant differences in the overall adverse events between baclofen and placebo. All reported side effects of baclofen were of mild-to-moderate intensity, and the drug was well tolerated.
  - Conclusion: "Abundant evidence suggests that baclofen may be a useful approach for the treatment of GERD patients; however, a larger well-designed research study would further confirm this recommendation."

Option #3: Consider a trial of pain modulators (eg, tricyclic antidepressant, selective serotonin uptake inhibitor, serotonin-norepinephrine reuptake inhibitors, or trazodone)

- Am J Gastroenterol. 2012 Nov;107(11):1662-7.

  Selective serotonin reuptake inhibitors for the treatment of hypersensitive esophagus: a randomized, double-blind, placebo-controlled study.
  - Methods: Patients with a normal distal esophageal acid exposure time, but with a positive SI were classified as having hypersensitive esophagus and were randomized to receive citalopram 20 mg or placebo once daily for 6 months.
  - Results: A total of 252 patients (150 females (59.5%); mean age 55 (range 18-75) years) underwent 24-h pH-impedance monitoring. Two hundred and nineteen patients (86.9%) recorded symptoms during the study day, while 105 (47.9%) of those had a positive SI (22 (20.95%) with acid, 5

(4.76%) with both acid and non-acid, and 78 (74.29%) with non-acid reflux). Among those 105 patients, 75 (71.4%) had normal distal esophageal acid exposure time and were randomized to receive citalopram 20mg (group A, n=39) or placebo (group B, n=36). At the end of the follow-up period, 15 out of the 39 patients of group A (38.5%) and 24 out of the 36 patients of group B (66.7%) continue to report reflux symptoms (P=0.021).

- Conclusion: "Treatment with SSRIs is effective in a select group of patients with hypersensitive esophagus."

Other options: Consider a prokinetic agent (e.g. metoclopramide) or a bile acid binder, such as cholestyramine or sucralfate

- World J Gastroenterol. 2014 Mar 7;20(9):2412-9.
  Addition of prokinetics to PPI therapy in gastroesophageal reflux disease: a meta-analysis.
  - Conclusion: "Combined therapy may partially improve patient quality of life, but has no significant effect on symptom or endoscopic response of GERD."

- Aliment Pharmacol Ther. 2005 Jul 15;22(2):79-94.
  Systematic review: proton-pump inhibitor failure in gastro-oesophageal reflux disease--where next?
  - Review article: Notes, reducing bile reflux in this patient population is desirable, but it is unclear if any available bile acid binders are sufficiently effective to improve symptoms

So… What does this all mean Jenn?

- There are options for refractory acid reflux. They include: adding a bedtime H2RA, adding baclofen, a SSRI, metoclopramide or a bile acid binder such as cholestyramine or sucralfate
- Really there isn't a ton of data to consider here, so:
  - In patients with persistent acid reflux on esophageal impedance pH testing or when testing is unavailable, and patients primarily report heartburn, considering first adding a bedtime H2RA
  - In patients with symptoms associated with non-acidic reflux on an esophageal impedance pH study or when testing is unavailable and patients primarily report regurgitation, consider baclofen
  - In patients with refractory GERD who have a normal esophageal impedance and pH study (esophageal hypersensitivity or functional heartburn), consider a trial of visceral analgesics (pain modulators), such as a SSRI
  - In patients with persistent GERD symptoms despite PPI therapy and delayed gastric emptying consider metoclopramide

Geriatric Considerations:

- As above older adults are at a higher risk of refractory acid reflux due to age and concurrent medical diagnoses
- Consider the recommendations as above

Stay tuned for future PCP Phast Phacts on acid reflux!

CLINICAL PEARL:
Options for refractory acid reflux include: bedtime H2RA, baclofen, a SSRI (i.e. citalopram), or metoclopramide. Consider potential etiologies.