PPI review: positioning Rabeprazole

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- PPIs are among the most widely used drugs for the treatment of gastro-oesophageal reflux disease (GORD) and the prevention of gastrointestinal (GI) bleeding.

- Challenge:
  - a PPI with minimal drug–drug interaction (DDI), especially in patients requiring polypharmacy.
  - Several PPIs are metabolized by the hepatic cytochrome P450 enzymes (mainly CYP 2C19 and 3A4)
    - All PPIs except for rabeprazole are extensively metabolized by and competitively inhibit CYP2C19 and CYP3A4

GORD Definition

- The Montreal consensus defines GERD as the reflux of stomach contents into the oesophagus causing ***troublesome*** symptoms and/or complications
  - not all 'troublesome' symptoms can be directly linked to reflux of gastric content, and
  - symptoms alone are insufficient for a conclusive diagnosis

- Objectively defined by the presence of characteristic mucosal injury seen at endoscopy and/or abnormal oesophageal acid exposure demonstrated on a reflux monitoring study

- In clinical practice, a distinction between the Non-Erosive Reflux Disease (NERD) and the Erosive Reflux Disease (ERD) is made. NERD is more common

GORD Presentation

- Typical symptoms
  - heartburn
  - chest pain
    - cardiac aetiology for chest pain is ruled out
  - regurgitation
- Both heartburn and chest pain can arise from motor disorders (such as achalasia)

- Regurgitation needs differentiation from rumination
  - Rumination is treated with behavioural therapy rather than acid suppression or antireflux surgery (ARS)
  - belching can trigger reflux
- Hoarseness, throat clearing and sore throat have even less robust reflux associations

- Epigastric and abdominal symptoms (nausea, abdominal pain) are unlikely to have a reflux aetiology
  - the exception being mischaracterisation of heartburn as epigastric burning

GORD Management

- The backbone of pharmacologic therapy for GORD are medications that are directed at neutralization or reduction of gastric acid
  - H2RA
    - Use at bedtime may be beneficial if dosed on an as-needed basis for patients with nocturnal symptoms and for patients with objective evidence of nocturnal acid reflux on pH monitoring despite PPI treatment
  - PPIs
    - Most commonly prescribed
    - Superior heartburn and regurgitation relief, as well as improved healing
    - Symptom relief and healing may not be rapid in EE

PPIs

- Bind only to proton pumps that are actively secreting acid
  - enteric- coated PPIs control intragastric pH best when given before a meal

- Maintenance PPI therapy should be administered for patients with GORD complications including severe EO (LA grade C or D) and Barrett's oesophagus

- For patients without EO or Barrett's oesophagus who continue to have symptoms when PPI therapy is discontinued, consideration can be given to on-demand therapy
  - Step-down therapy to H2RAs is another acceptable option for management, particularly in patients with NERD

PPI in PUD

- PUD commonly associated with HP infection and/ or NSAID use

- Antibiotics alone are ineffective in eradicating H. pylori.
  - A combination of adequate acid suppression and antibiotic therapy is necessary for the successful eradication of H. pylori

- NSAIDs cause peptic ulcers by inhibiting prostaglandin synthesis and weakening gastro-duodenal mucosal defenses
  - PPIs are the treatment of choice for large or complicated ulcers
  - PPIs may also be used for prevention of NSAID–induced ulcers

D-D-I

- PPIs cause significant increases in gastric pH
  - may alter the absorption of weak acids or bases.
  - may inhibit the absorption of drugs such as griseofulvin, ketoconazole, itraconazole, iron salts, vitamin B12
  - Coadministration with these agents should be approached cautiously

- PPIs are metabolized to varying degrees by the hepatic cytochrome P450 enzymatic system
  - may alter drug metabolism by induction or inhibition of the cytochrome P enzymes.
    - This is an important consideration in patients taking medications with a narrow therapeutic window
      - such as diazepam (Valium), phenytoin (Dilantin), and warfarin (Coumadin).

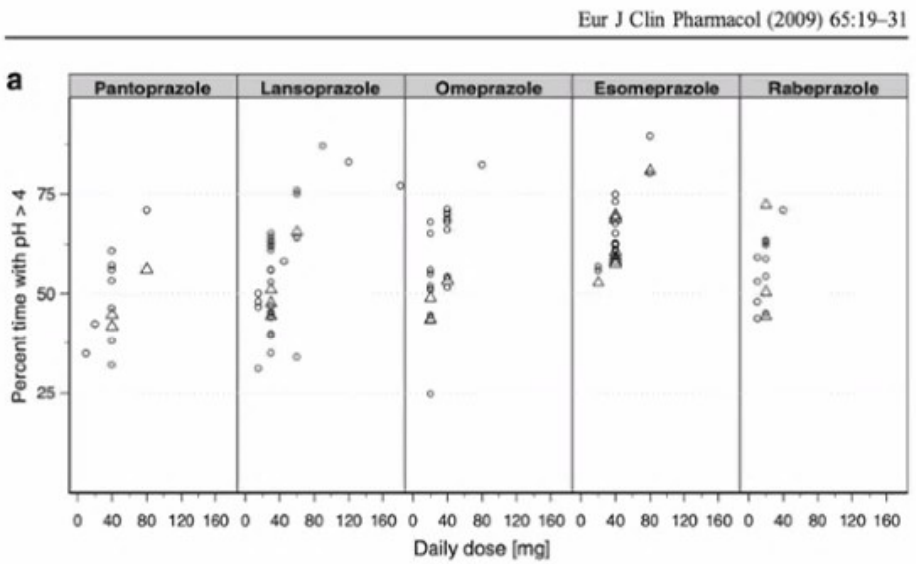
PPI therapeutic efficacy

mean pH over time (typically mean 24-h pH)

- Based on the mean 24-h gastric pH, the relative potencies of the five PPIs compared to omeprazole were*

PPI	Relative potency
Pantoprazole	0.23
Lansoprazole	0.90
Omeprazole	1.00
Esomeprazole	1.60
Rabeprazole	1.82

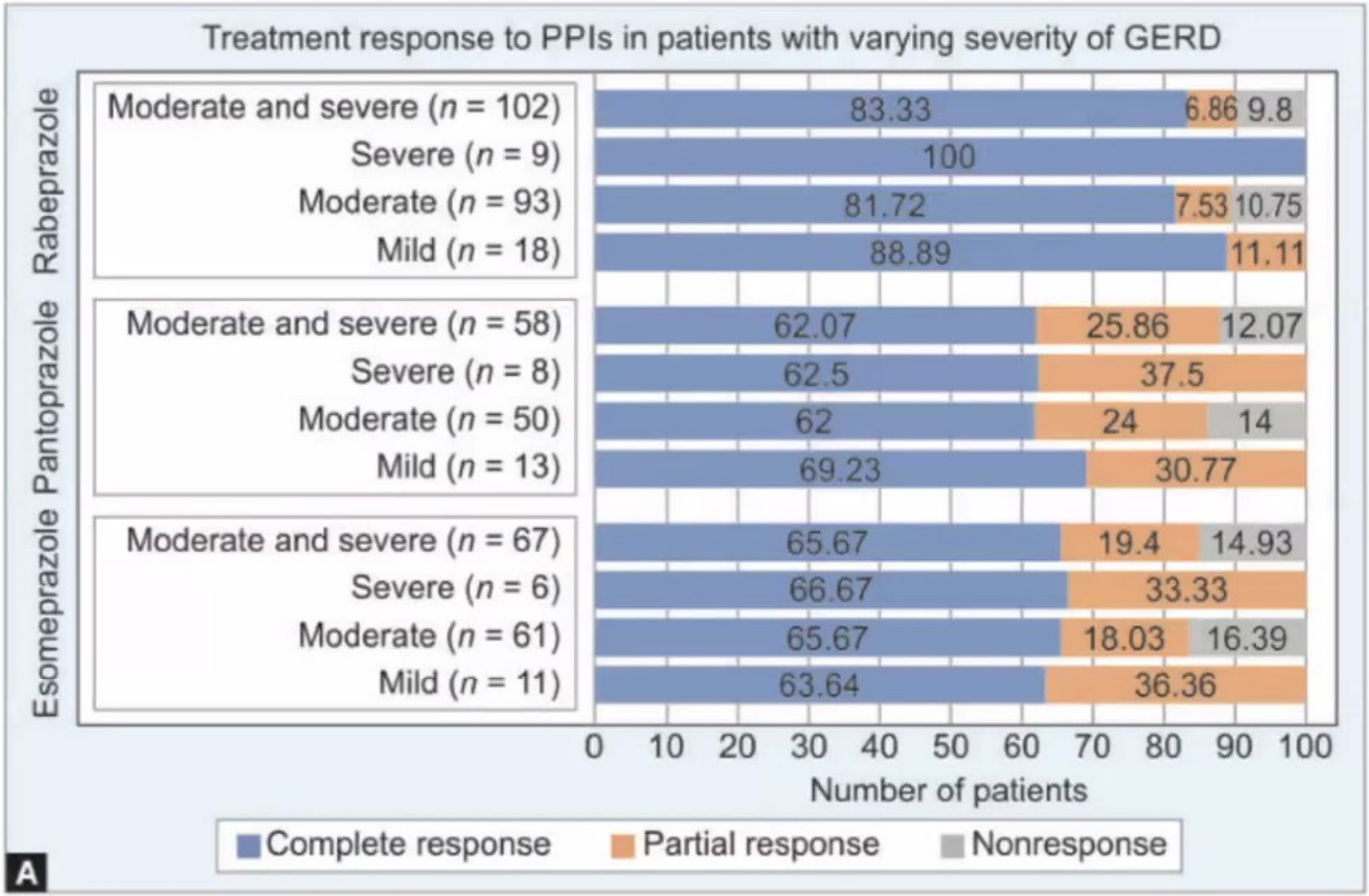
percentage of time with pH > 4

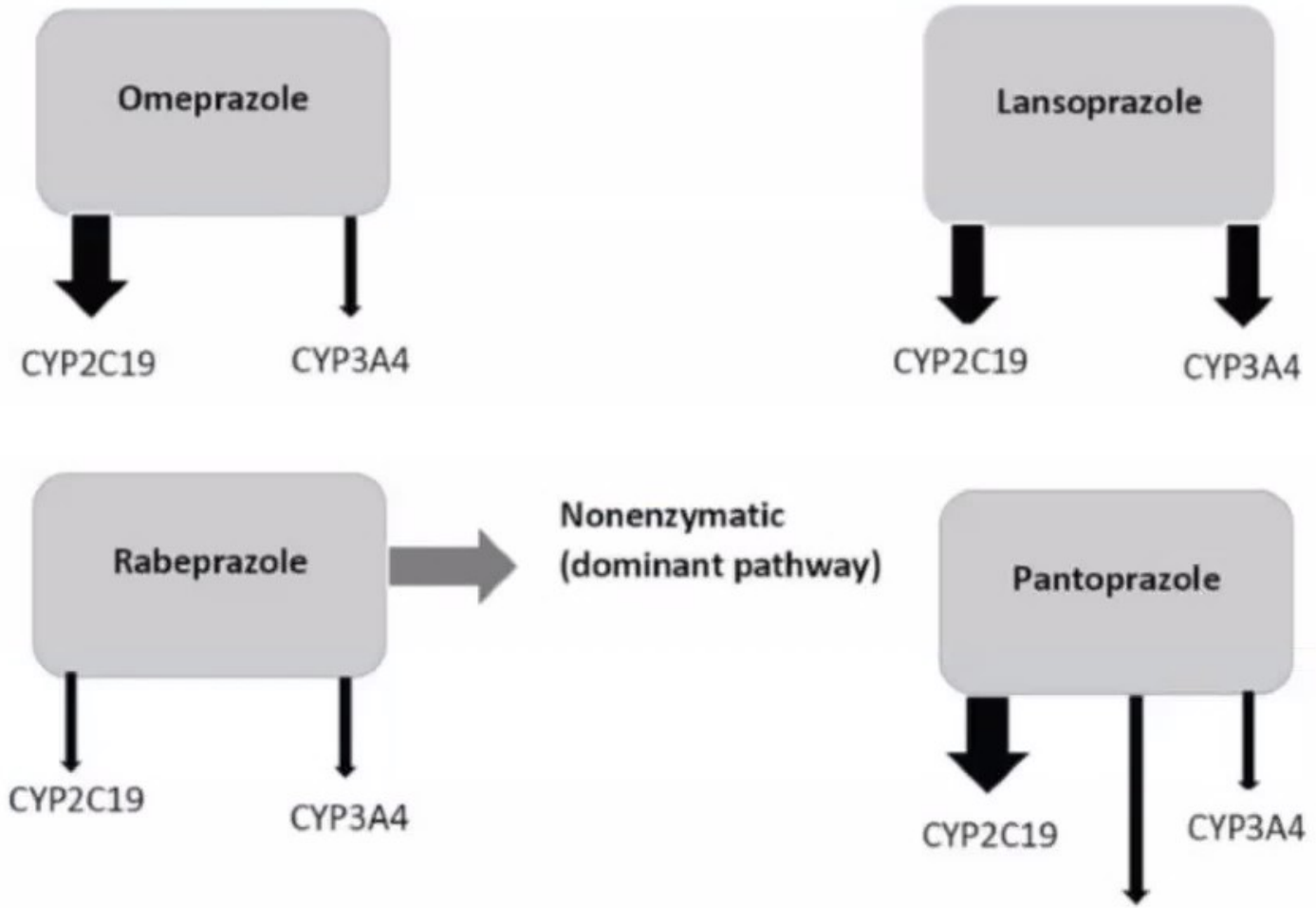


*Eur J Clin Pharmacol (2009) 65:19–3

Dosage equivalents

Drug	WHO	CAG	FDA	
Omeprazole	20	20	20	
Esomeprazole	30	40	20	
Lansoprazole	30	30	15	
Pantoprazole	40	40	40	
Rabeprazole	20	20	20	


Treatment response to PPIs in patients with varying severity of GERD
Rabeprazole
Moderate and severe (n = 102)
83.33
6.86
9.8
Severe (n = 9)
100
Moderate (n = 93)
81.72
7.53
10.75
Mild (n = 18)
88.89
11.11
Pantoprazole
Moderate and severe (n = 58)
62.07
25.86
12.07
Severe (n = 8)
62.5
37.5
Moderate (n = 50)
62
24
14
Mild (n = 13)
69.23
30.77
Esomeprazole
Moderate and severe (n = 67)
65.67
19.4
14.93
Severe (n = 6)
66.67
33.33
Moderate (n = 61)
65.67
18.03
16.39
Mild (n = 11)
63.64
36.36
0 10 20 30 40 50 60 70 80 90 100
Number of patients
Complete response
Partial response
Nonresponse
A

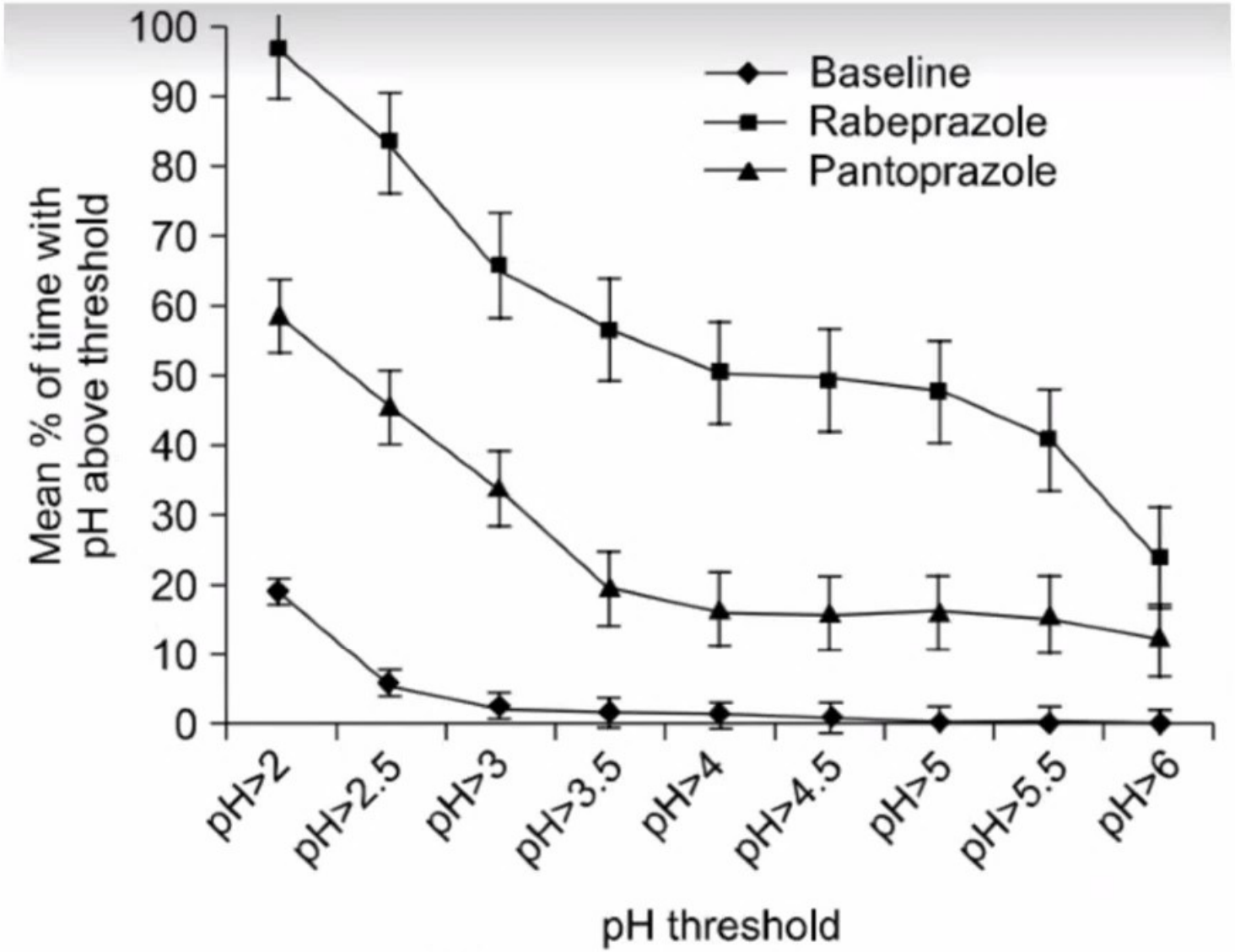


Cardiol Ther (2023) 12:557–570

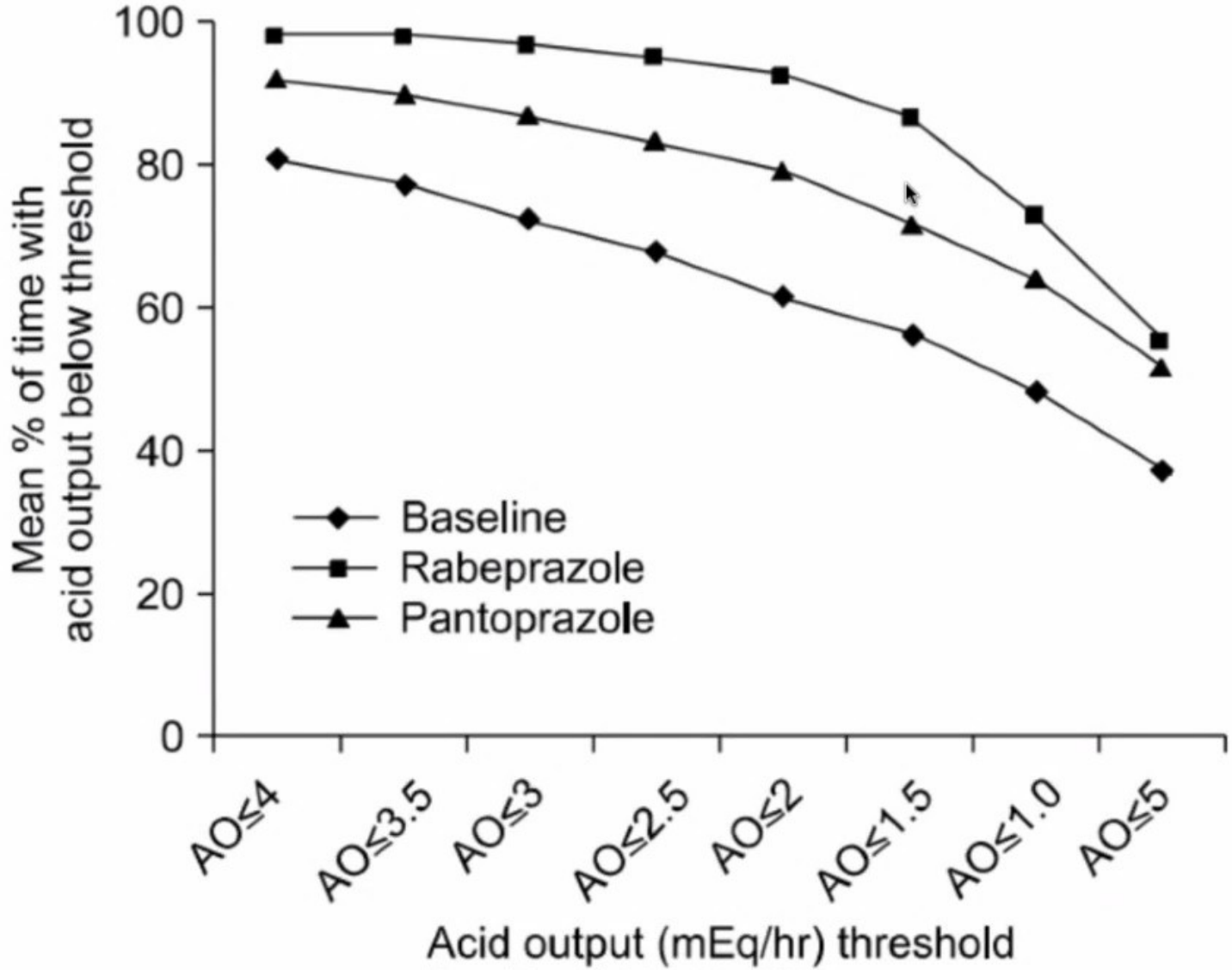
Rabeprazole

- Rabeprazole has been shown in vitro to be more readily converted to its active form than omeprazole, pantoprazole or lansoprazole.
- In addition, rabeprazole is known to have a faster onset of action in patients with heartburn leading some to suggest that rabeprazole may have efficacy as an on-demand or abortive therapeutic agent.
- Oral rabeprazole sustained a significantly greater percentage of time during which mean pH was greater than 4.0 compared to oral pantoprazole (50.2% vs 16.0%).*
- Overall, rabeprazole maintained mean pH at every threshold measured for a greater percentage of time as compared to pantoprazole*

*Gut and Liver, Vol. 2, No. 1, June 2008



*Gut and Liver, Vol. 2, No. 1, June 2008



*Gut and Liver, Vol. 2, No. 1, June 2008

Rabeprazole

- Rabeprazole has the highest pKa (acid stability) of all PPIs
  - is more rapidly converted to inhibit the proton pump as compared to omeprazole, lansoprazole or pantoprazole.
  - targets a greater population of parietal cells to give a more rapid and pronounced degree of acid inhibition
- In addition, rabeprazole may have more prolonged and potent acid inhibitory effects due to continued binding to proton pump transmembrane domains even after achieving 100% inhibition of ATPase activity
- metabolism is largely nonenzymatic and therefore less dependent on CYP2C19, giving a greater consistency of pharmacokinetics across all patients, regardless of CYP2C19 genotype

Back to GORD

- The onset of action, degree and duration of acid suppression with proton pump inhibitors are relevant to the treatment of acid-related disorders
  - OOA: Acid suppression of first day of dosing
  - dº AS: Intragastric pH
  - Dº AS: Time at pH >4 during the 24 hour period post dosing

- In gastro-oesophageal reflux disease, rapid acid suppression is important for effective pain relief at the onset of treatment
- Rapid acid control may also be of clinical advantage in Helicobacter pylori treatment regimens with acid-sensitive antibiotics

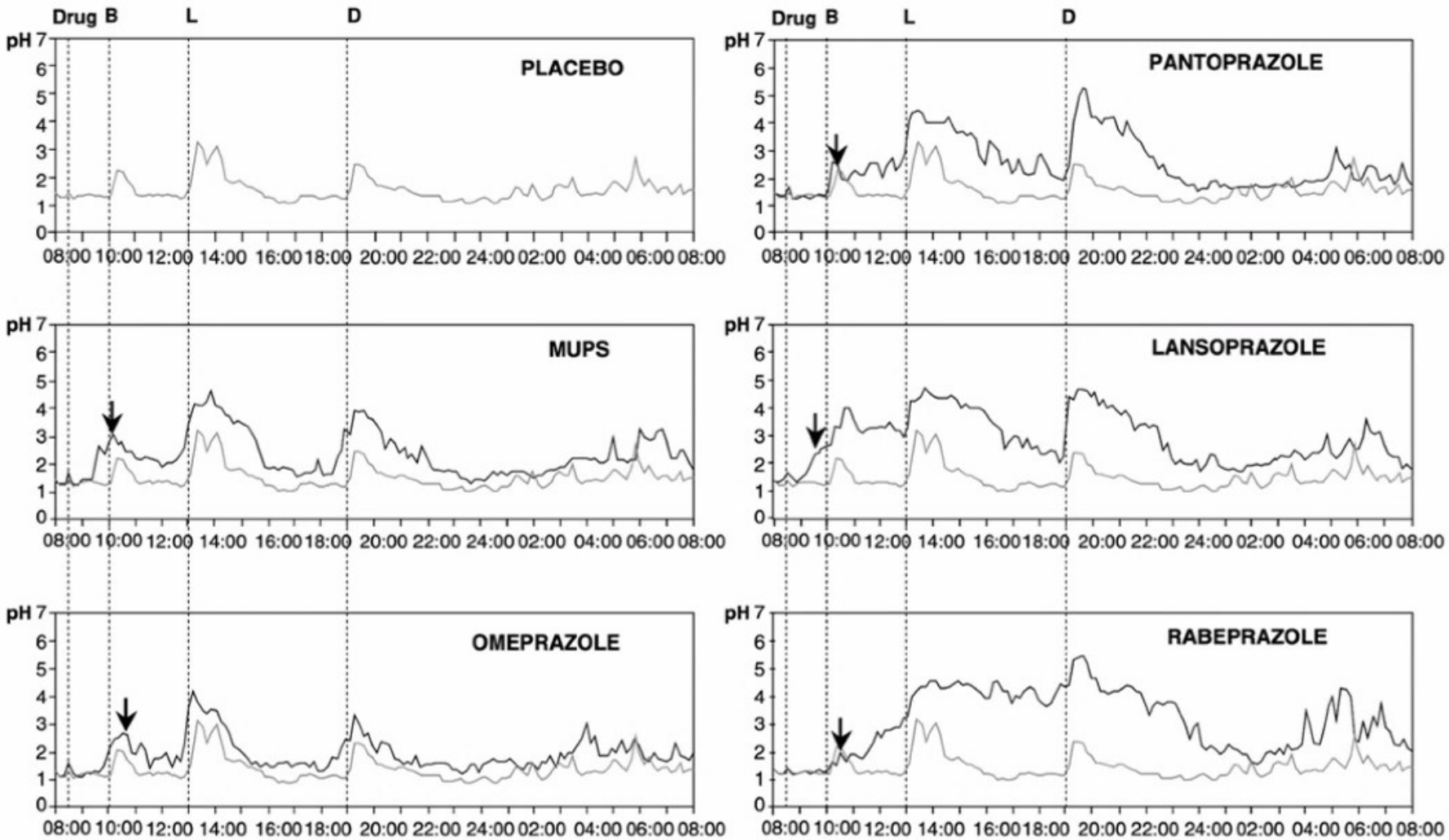


Figure 1. Median 24-h pH monitoring profiles on the first day of proton pump inhibitor treatment. Drug, drug administration; B, breakfast; L, lunch; S, supper. Arrows indicate the onset of antisecretory action.

Duration of acid suppression

- On first day post dosing

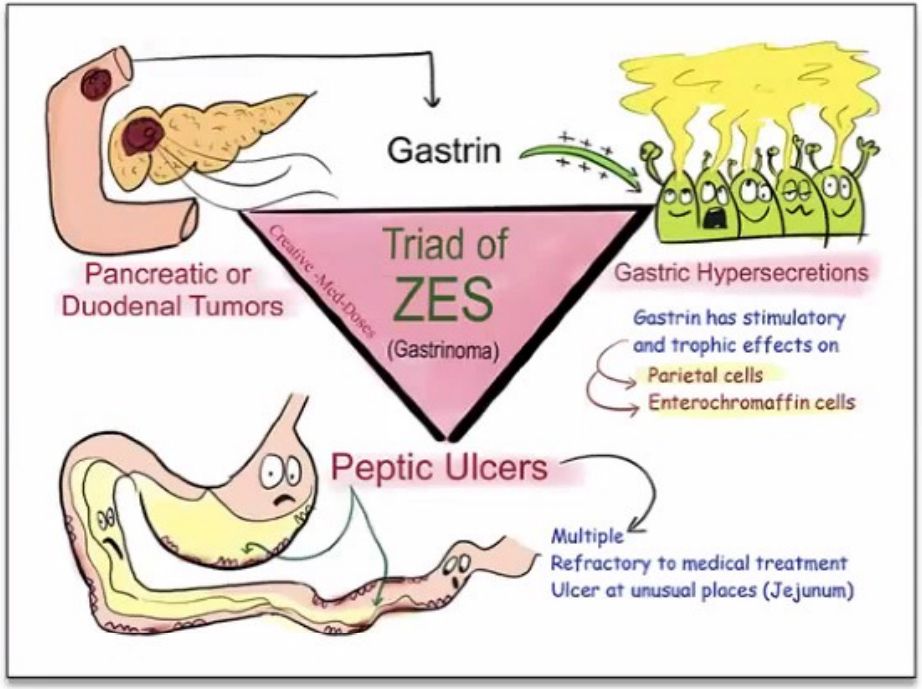
				OME		
pH	RAB	LAN	PAN	CAPS	MUPS	PBO
pH > 3	13.1 (16.4–17.1)†‡§¶	11.2 (7.3–15.7)†‡¶	6.9 (1.0–15.2)¶	5.8 (2.3–12.8)¶	5.7 (0.9–16.4)¶	2.7 (1.0–5.8)
pH ≥ 4	8.0 (3.5–13.1)*†‡§¶	7.4 (3.4–11.1)†‡¶	4.9 (0.5–12.8)¶	2.9 (0.6–8.6)¶	3.0 (0.3–12.1)¶	0.9 (0.3–3.7)

CAPS, capsule; LAN, lansoprazole; MUPS, multiple unit pellet system; OME, omeprazole; PAN, pantoprazole; PBO, placebo; RAB, rabeprazole.

Aliment Pharmacol Ther 2003; 17: 1507–1514

RABEPRAZOLE

- Indications
  - Active duodenal ulcer
  - Active benign gastric ulcer
  - Symptomatic erosive or ulcerative GORD
  - Maintenance treatment of healed erosive or ulcerative GORD (12 months)
  - Symptomatic treatment of GORD
  - Zollinger-Ellison Syndrome and other pathological hypersecretory conditions
  - *H. pylori*-positive duodenal ulcers



Text: SAHPRA-approved PI for Originator dated 17 March 2022. Picture: https://creativemeddoses.com/topics-list/zollinger-ellison-syndrome-zes/.

PROTON PUMP INHIBITORS

- Equivalent PPI doses

PROTON PUMP INHIBITOR	FULL STANDARD DOSE	LOW DOSE (ON-DEMAND)	DOUBLE DOSE
Esomeprazole	20 mg once daily	Not available	40 mg once daily
Lansoprazole	30 mg once daily	15 mg once daily	30 mg twice daily
Omeprazole	20 mg once daily	10 mg once daily	40 mg once daily
Pantoprazole	40 mg once daily	20 mg once daily	40 mg twice daily
Rabeprazole	20 mg once daily	10 mg once daily	20 mg twice daily

Text: SAHPRA-approved Professional Information for each of the respective products. Kheloussi S; Appropriate use and safety concerns of proton pump inhibitors; US Pharmacist; 16 Jun 2017; available from https://www.uspharmacist.com/article/appropriate-use-and-safety-concerns-of-proton-pump-inhibitors; Pictures: MacLeods.

PROTON PUMP INHIBITORS

- Rabeprazole advantages
  - Preferred option in CV patients requiring clopidogrel or with polypharmacy
    - Lowest risk with clopidogrel
      - NICE guidance says to avoid omeprazole/esomeprazole
    - Optimal acid suppression
  - Stronger inhibition of gastric acid secretion
    - Particularly during night
    - RCT that look at acid suppression following first day of dosing
      - Outperformed lansoprazole, pantoprazole, omeprazole

Text: Ohning GV, et al; Rabeprazole is superior to omeprazole for the inhibition of peptone meal-stimulated gastric acid secretion in Helicobacter pylori-negative subjects; Alimentary Pharmacology & Therapeutics; 2003 May 01; 17(9): 1109–1114. Wang HS, et al; Comparative efficacy of rabeprazole and pantoprazole in the control of nocturnal acid output and intragastric acidity; Gut Liver; 2008 Jun; 2(1): 30-38. Warrington S, et al; Effects of rabeprazole, 20 mg, or esomeprazole, 20 mg, on 24-h intragastric pH and serum gastrin in healthy subjects; Alimentary Pharmacology & Therapeutics; 2002; 16:1301-1307. Saitoh T, et al; Effects of rabeprazole, lansoprazole and omeprazole on intragastric pH in CYP2C19 extensive metabolizers; Alimentary Pharmacology & Therapeutics; 2002; 16: 1811-1817. Dalal J, et al; Cardiovascular compatibility of proton pump inhibitors: Practice Recommendations; Cardiology Therapy; 2023; 12: 557-570.
Picture: https://www.vectorstock.com/royalty-free-vector/celebrating-success-achievement-and-jubilation-vector-36447017.

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