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REVIEW ARTICLE

In search of the grail: A race for acid suppression☆

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Abstract Proton pump inhibitors are the reference standards for the treatment of acid-related diseases. Acid suppression in gastroesophageal reflux disease is associated with a high rate of mucosal cicatrization, but symptom response differs among endoscopic phenotypes. Extraesophageal manifestations have a good clinical response in patients that present with abnormal acid exposure (diagnostic test) in the esophagus.

Proton pump inhibitors have shown their effectiveness for reducing symptom intensity in nighttime reflux and sleep disorders, improving quality of life and work productivity. That can sometimes be achieved through dose modifications by splitting or increasing the dose, or through galenic formulation.

Proton pump inhibitors are not exempt from controversial aspects related to associated adverse events. Technological development is directed at improving proton pump inhibitor performance through increasing the half-life, maximum concentration, and area under the curve of the plasma concentrations through galenic formulation, as well as creating safer and more tolerable drugs.

The present review is focused on the mechanisms of action, pharmacokinetic properties, and technological advances for increasing the pharmacologic performance of a proton pump inhibitor.

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PALABRAS CLAVE
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La búsqueda del Grial: una carrera por la supresión ácida

Resumen Los inhibidores de la bomba de protones (IBP) son el estándar de referencia para el tratamiento de las enfermedades relacionadas con el ácido. En la enfermedad por reflujo gastroesofágico (ERGE) la supresión ácida se asocia con una alta tasa de cicatrización de la mucosa; sin embargo, la respuesta sintomática difiere entre los fenotipos endoscópicos. Las manifestaciones extraesofágicas tienen buena respuesta clínica en quienes presentan una exposición anormal al ácido (prueba diagnóstica) en el esófago.

Los IBP han demostrado su efectividad para disminuir la intensidad sintomática en el reflujo nocturno y en los trastornos del sueño, mejorando la calidad de vida y la productividad laboral. Esto se logra, en ocasiones, mediante las modificaciones al fraccionar o aumentar la dosis, así como la galénica.

Estos fármacos no están exentos de aspectos controversiales en relación con los eventos adversos asociados. El desarrollo tecnológico está encaminado a mejorar el rendimiento del IBP mediante el incremento de la vida media, la concentración máxima y el área bajo la curva de las concentraciones plasmáticas mediante la galénica, y por otra parte a crear fármacos más seguros y tolerables.

En esta revisión nos enfocamos a los mecanismos de acción, las propiedades farmacocinéticas y los avances tecnológicos para incrementar el rendimiento farmacológico de un IBP.

Introduction

Burimamide (1972) was the first H2-receptor antagonist (H2RA) validated in humans. The prototype was cimetidine, discovered in 1976, followed by ranitidine (1981), famotidine (1981), and nizatidine (1987).[1–3]

The race to suppress acid with proton pump inhibitors (PPIs) began with the discovery of timoprazole (1975),[2] which was associated with toxicity (thyromegaly and atrophy of the thymus),[3] and developed with omeprazole (1979), upon modifying the benzimidazole ring.[4] Nevertheless, concern about the effects of prolonged suppression limited the initial dose (20 mg).[4,5] Later, lansoprazole 30 mg (1995), rabeprazole 10 mg (1999), and pantoprazole 40 mg (2000) appeared.

The plasma half-life (t1/2) of PPIs is 1-1.5 h.[6] They are racemates with two molecularly equal isomers (left-levogyre and right-dextrogyre) with the same chemical formula, but different structures, properties, and configurations. The s-enantiomer (levogyre) of omeprazole, esomeprazole (2000), was created through isomerism.[6]

The addition of a sodium bicarbonate layer to omeprazole (2006) achieved rapid gastric alkalinization, proton pump (PP) activation, and its increased absorption, reflected in maximum concentration [C_{max}].[7] Dexlansoprazole (R-lansoprazole) was created by turning the molecule of lansoprazole; its performance increased by adding a dual release system that produced a greater area under the plasma concentration curve [AUC_{24}].[8]

PPIs are the third highest selling class of drugs worldwide and they have not been exempt from controversy, with respect to their safety. More than 21 million people received a prescription in the United States and annual sales were reported at 13.9 billion USD.[9,10] In 2010, manufacturers were required by the Food and Drug Administration (FDA) to warn about the associated risk for fractures,[11] then for hypomagnesemia,[12] cardiovascular adverse events (CVAEs) (2013),[13] dementia,[14] chronic kidney disease,[15] community-acquired pneumonia,[16] and osteoporosis (2016).[10]

Vaezi et al.[17] stated that it is the responsibility of researchers and the media to prevent an ''anxiety epidemic'', exhorting a ''more critical and responsible approach so that weak results are not presented to the public as facts''.

The evidence on those causal associations is very weak, with inconsistencies in the effect size due to methodological designs. For example, the risk for CVAEs was greater in observational studies, compared with randomized studies (OR 1.25 vs. 0.89, p = 0.85).[18] Table 1 summarizes the effect size calculations in relation to the adverse events.

The strength of association (Hill Criteria) evaluates causality in observational studies. We can see that even though the results in the majority of studies show statistical significance ($p < 0.05$), the odds ratio (OR) is < 3.0, with broad 95% confidence intervals (95% CI), signifying great heterogeneity among data or a small sample size.

An OR > 3.0 is likely to signify a causal association, but most reports fall into areas of ''potential bias'' (0.33-3.0). Importantly, the majority of natural phenomena are multifactorial, thus, the modest effect size is not surprising.[17,19] In general, adequate use (approved indications) of the lowest effective dose has been recommended, as well as not increasing the dose or maintaining continuous therapy in PPI nonresponders.[20]

As an analogy, the race for acid suppression is a fight between different medieval knights, with all the available weapons (structure, dose, isomerism, release mechanisms,

Table 1 The most recent size of effect calculations.

Adverse event heterogeneity	Size of effect (95% CI)	
Enteral infection	OR 2.55 (1.53-4.26)	Yes
Community-acquired pneumonia	OR 1.49 (1.16-1.92)	Yes
Clostridium difficile diarrhea	OR 1.26 (1.12-1.29)	Yes
Hip fracture	OR 1.26 (1.16-1.36)	Yes
Dementia	HR 1.44 (136-1.52)	N/A
Vitamin B12 deficiency	HR 1.83 (1.36-2.46)	Borderline
Chronic kidney disease	RR 1.36 (1.07-1.72)	Yes
Myocardial infarction	OR 1.16 (1.09-1.24)	N/A

OR: odds ratio; RR: relative risk
Source: Laheij et al.[16]

etc.) to reach the fort (the parietal cell) where the Holy Grail (the acid-secreting enzyme) is hidden.

Acid secretion: an acid universe

The enteric nervous system is the neural network that innervates the stomach and is composed of the myenteric plexus (Auerbach's plexus) and the submucosal plexus (Meissner's plexus). The afferent (80-90%) and efferent (10-20%) fibers of the vagus nerve interact with the parasympathetic control of the heart, lungs, and digestive tract.[21–23]

The cephalic phase of acid secretion, mediated by cholinergic and vagal mechanisms, begins with the mere sight, thought, taste, or smell of food and with swallowing. It is a reflex action; ''everything passes through the senses''. In the gastric phase, maximum secretion is produced, involving the vagus nerve and gastrin. Vagal afferent nerve endings detect food and gastric distension releases acetylcholine by stimulating the receptors.[23]

The parietal cell: origin of the acid

The parietal cell (PCel) secretes hydrochloric acid (HCl) and intrinsic factor.[24–26] Acid secretion is produced in response to neurocrine, paracrine, and endocrine stimuli. Basolateral membrane receptors respond to histamine (H), acetylcholine, and gastrin stimuli. Gastrin activates the enterochromaffin-like cells, releasing H that stimulates the PCel, activating adenylyl cyclase to generate cyclic AMP (3',5'-cyclic adenosine monophosphate). H changes the morphology of the PCel in the resting state, so that it becomes active. Cytosolic vesicles that contain the H+,K+-ATPase enzyme fuse with the apical membrane, exposing it to the canaliculus.[25,26]

The H^+,K^+-ATPase enzyme opens the gateway and the acid is produced

That $\alpha\beta$-heterodimeric enzyme has two components. The site that increases chemical reaction rate (catalytic<) is in the α subunit (PM $\sim$ 100 kDa). The amino acid, Asp386, is the ATP-binding site for phosphorylation.[15] The enzyme has a high affinity for the H^+ of the cytoplasmic side (E1 conformation).

The initial step is the reversible binding of ATP to the enzyme (in the absence of K^+). The transfer of the gamma-phosphate of ATP to the Asp386 site of the catalytic subunit (E1-P·H+) is mediated by Mg2+. The next step is E2 conformation (E1P H3O+ to E2P H3) with high affinity for K+ and low affinity for H3O+. That process releases H3O+ and increases the binding to K+.[15]

The great dragon awakes: acid secretion

Acid secretion is produced by the ionic exchange of the intracellular H+ for luminal K+. For each H+ transported to the canaliculus (H+, K+-ATPase), the membrane transporter, CL-HCO3 delivers HCO3- to the plasma and Cl- to the cytosol.[33,34] Cl- acts as a counterion of the K+ flow, balancing the charges (electroneutral secretion). Stimulation of the H+,K+-ATPase enzyme is the final step in acid secretion.[25]

Normal subjects have a nocturnal increase (10:00 pm-2:00 am) in acid secretion, which is continuous with great variations from night to night and from subject to subject.[26] Acid secretion is minimal during wakefulness, if there is no meal stimulation. In contrast, there is an increase in secretion volume and concentration in the case of duodenal ulcer. However, there is no correlation between the stages of sleep and acid secretion and concentration.[15,27,28] The mealtime schedule is the main regulating clock for acid secretion.

Proton pump inhibitors

The molecular target

The molecular target of PPIs is the H+,K+-ATPase enzyme, which they block. Pharmacokinetic properties (bioavailability, metabolism, and genetic variability) affect their pharmacologic performance. The protonation (the addition of H+) in an acid environment is necessary for the activation of those prodrugs. The delayed release and longer half-life (t1/2) improve performance (bioavailability) by increasing the AUC_{24}.[29–32]

PPIs are metabolized by CYP2C19 and CYP3A4, and so the factors that interfere with enzyme activity, affect the AUC. CYP2C19 variations are the most important pharmacogenetic factor that affect response.[33]

Mechanisms of action

Those weak bases have a pyridine ring and another benzimidazole ring bound by a methylsulfinyl group with variations (side ring).[34] The enteric lining is dissolved, and the drug absorbed upon reaching the duodenum (pH > 5.6). The non-protonated molecule (ionized) can freely penetrate the lipid membranes. The pKa is the pH at which half of the molecule is ionized and the other half is not.[35]

That prodrug is selectively accumulated in the PCel. It is the only behavior of the organism surrounded by a membrane with a pH < 4, in which the pH is 1,000 times more acid than blood.[26,27] Accumulation is determined by its pKa1 (~ 4 omeprazole, lansoprazole, and pantoprazole, ~ 5.0 rabeprazole, and 5.38 ilaprazole).[35–37]

The first protonation (pyridine) results in the molecule remaining trapped inside the PCel. Acid stability depends on the pKa1. The lower pK1 of pantoprazole confers greater stability upon it (pantoprazole 3.83, omeprazole 4.0, lansoprazole 3.83, and rabeprazole 4.53).[38,39] The reaction with the cysteines is produced during the second protonation (N imidazole 2C-benzimidazole) in the canaliculus (pH < 1) at a pKa2 ~1.[38,39] Due to rabeprazole's pKa2 (0.6), its activation is greater.[40–42]

The activation rate is dependent on protonation. The pKa and pH influence acid accumulation, activation, and stability.[34,35] Suppression is achieved through the binding of the active molecule to the covalent disulfide bonds (S = S) of cysteine.[38,41,42]

PPI ingestion (30 to 60 min) before the first meal of the day ensures that a greater number of proton pumps (PPs) are active. Intragastric pH is greater after breakfast than after supper (5.0 vs. 4.5, p < 0.01). The Cmax and AUC of lansoprazole and esomeprazole decrease with food, unlike pantoprazole, omeprazole, and rabeprazole.[37]

Binding to cysteines in the transmembrane (TM) domain of the PCel

The active molecule forms stable bonds with two cysteines (Cys321, Cys813, Cys822, or Cys892). All PPIs bind to Cys813 (TM 5 and 6), fixing the enzyme (E2 configuration); the selectivity for the other cysteine is variable.[31] Omeprazole, lansoprazole, and rabeprazole bind to Cys892, whereas lansoprazole and rabeprazole bind to Cys321. Due to the fact that pantoprazole binds in the other 50% to Cys822, located in the deepest TMs, the S = S bonds remain stable because they are not accessible to the reducing effect of gluthatione.[31,32]

If the recovery of acid secretion were due to the synthesis of new PPs upon suspending the PPI, then suppression time would be close to the t1/2 of the PP (~ 48 h). Even though S = S bonds are thought to be stable, acid recovery varies among PPIs, suggesting that pump t1/2 recovery is different,[40] being faster with lansoprazole (~ 13 h) and omeprazole (~ 27 h) than with pantoprazole (~ 46 horas), which is closer to the expected time (54 h) if *de novo* synthesis were the only restoration mechanism.[41–44]

Other factors interfere with secretion inhibition: 1) PP, 2) continuous *de novo* synthesis (25%/day), and 3) partial reversal of the S = S bonds with some PPIs.[25,26,45]

Stability in the PPI acid medium

Approximately 3 days are needed to reach a stable inhibitory status, that is to say, to reach the balance between active PP inhibition and inactive PP stimulation, upon the disappearance of the PPI from the blood and *de novo* pump synthesis.[46]

One dose inhibits up to 66% of acid secretion, given that ~ 70% of the active PPs are available. Once the optimum dose is reached, increasing the dose does not influence effectiveness, unlike increasing dose frequency.[46]

With food, ~ 80% of active PPs can be inhibited (the first PPI dose). On the second day, there are new PPs plus more than 20% of uninhibited PPs from the first day. The balance repeats itself, until reaching a stationary pharmacodynamic state (an equal number of inhibited PPs and synthesized PPs).[43]

The t1/2 of the PP in the rat is ~ 54 h. Twenty percent of the new PPs are synthesized, mainly at night. The bedtime PPI dose does not increasingly inhibit nocturnal acid breakthrough, because the drug has disappeared by the time there is nighttime secretion.[44,45]

A brief explanation of pharmacokinetics and pharmacodynamics

Pharmacokinetics deals with what happens to the drug (concentration) from the time it is administered (dose), to its complete elimination from the body. Pharmacodynamics is the study of what happens to the organism due to the action of the drug.[46–48]

The physicochemical characteristics, pharmaceutical form, absorption site, elimination site, and the ''first hepatic step'' influence absorption. PPIs are weak, ionized (polar), water soluble (permeable) bases that become liposoluble (non-ionized and nonpermeable) upon activation.[46,47]

A base with a lower pKa is weaker and is better absorbed in the intestine (> pH). In an acid environment, the base increases the number of non-ionized molecules upon accepting protons. The pKa is the pH at which half of an acid's molecules give up their protons.[37,47,49,50]

The enteric layer (pH-sensitive/time) prevents degradation or activation, protecting the nucleus of the acid for its delivery at a determined site.[51–54] Several factors influence recovery behavior:[55,56] a) polymer (pH-threshold); b) composition; c) nucleus and swelling, disintegration, and natural properties (dosage); d) imperfections (integrity); e) layer thickness; f) *in vitro* test conditions (composition, pH, ionic strength, and stirring intensity); and g) gastric conditions.

PPIs are transported in the blood (plasma, erythrocytes, or proteins) for their distribution, which is dependent on their protein binding (omeprazole 95%, esomeprazole 97%, lansoprazole 97%, dexlansoprazole 96%, pantoprazole 98%, and rabeprazole 96.3%).[57,58]

Chemical transformations reduce the liposolubility and biologic activity of PPIs. Enzymes modify the PPI molecule through chemical reactions classified according to their functionalization (phase 1) or through biosynthesis (phase 2).[57,58]

- *Phase 1 reactions (oxidation and hydrolysis)*. Activity loss is produced upon introducing or exposing a functional group producing more polar substances. The most important reaction is oxidation.
- *Phase 2 reactions (conjugation with glucuronide acid, glycine, or acetic acid)*. A drug or metabolite binds to a substrate. The S = S bond between the functional group (drug) and glucuronide acid, sulfates, amino acids, or acetate produces highly polar inactive compounds that are excreted through urine and stools.

Cytochrome p450

Cytochrome p450 belongs to the family of heme proteins that absorb light (450NM). The majority of commonly used drugs are biotransformed by CYP3A4 (50%), CYP2D6 (20%), and CYP2C9 and CYP2C19 (15%).

Inhibition or induction of the metabolic interactions of one or more enzymes depends on the dose and bond to the enzyme.[30] To predict the effect of tissue concentrations, the plasma concentrations of the drug are calculated[47,48] (fig. 1).

Latent period

The latent period is the amount of time from ingestion to the beginning of the pharmacologic effect, that is to say, the maximum expected concentration (fig. 1).

Bioavailability (available fraction)

Bioavailability is the speed at which the unaltered quantity of the drug enters the systemic circulation. A drug's bioavailability is measured through the AUC_{24}.[48]

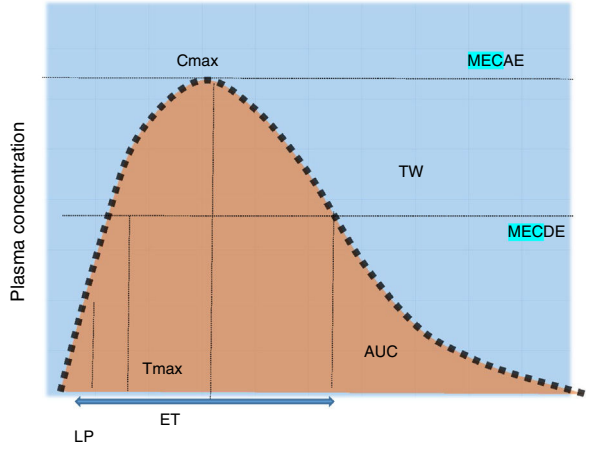

Figure 1 Plasma concentration of the drug and effects.
Plasma concentration
AUC: area under the curve; Cmax: maximum concentration; ET: exposure time; LP: latent period; MECAE: minimum effective concentration of the adverse event; MECDE: minimum effective concentration of the desired effect; Tmax: maximum time; TW: therapeutic window.Source: Armijo.[47].

Plasma half-life (t1/2) in hours

The time it takes for the drug's concentration to decrease to half the original amount. If the t1/2 is low, the drug should be administered more frequently. Four or 5 days are needed to reach the steady state, given that the time it takes to decrease from 150 mg to 75 mg is the same it takes to decrease from 50 mg to 25 mg. In other words, 50% is eliminated after one half-life, 75% after 2 half-lives, 87.5% after 3 half-lives, and > 95% after 4-5 half-lives.[40,47–49]

Maximum concentration [C_{max}] μg/ml

The pharmacokinetic measurement that determines dose. It is the absorption velocity.[51–53]

Area under the plasma concentration curve

The plasma concentration of the drug or AUC_{24} (μg h/ml). The equimolar formulations can have different AUC_{24} with similar absorption velocity or similar AUC_{24} and different absorption velocity.[54,55]

After repeated administration, PPIs with nonlinear pharmacokinetics (omeprazole and esomeprazole) have reduced clearance (⇑ AUC_{24}) due to CYP2C19 inhibition. The other PPIs have linear pharmacokinetics.[56–59]

PPI efficacy in gastroesophageal reflux disease

Gastroesophageal reflux disease (GERD) consists of the return of gastric content into the esophagus, causing symptoms that affect quality of life, with or without complications.[60] According to the Montreal Consensus, it is classified into: 1) esophageal syndromes: symptomatic or with damage to the mucosa and 2) extraesophageal syndromes: with an established or proposed association.[61]

Diagnostic test with a PPI

In the absence of alarm symptoms, the PPI therapeutic trial is the initial test for treating typical GERD symptoms.[19] However, specificity (17-29%) and the likelihood coefficient (+) (0.5 to 1.5) for diagnosis are suboptimal[62] because response does not make or rule out the diagnosis. The PPI changes the pH (refluxate) but does not have a direct effect on reflux.[63,64] In uninvestigated heartburn, the response to a PPI (8 weeks) is 70%, with a number needed to treat (NNT) of 2.2 for symptom improvement.[65]

Erosive and nonerosive esophagitis

PPI effectiveness has been demonstrated at 86% cicatrization (NNT = 1.8)[66] and 72% symptom response.[67,68] They have also been shown to be more effective than H2ARs and prokinetics (RR 0.37 vs. 0.77 vs. 0.86), regardless of severity, dose, and treatment duration.[69] In nonerosive reflux disease (NERD), the RR was 0.73 (PPI), 0.84 (H2AR), and 0.72 (prokinetic).[70]

Symptom response (EE 56% vs. NERD 37%; p = 0.0001) and therapeutic gain in GERD symptoms was greater for the

erosive phenotype (−48%[95% CI: 24.6-93.8] vs. 27.2% [20.9-35.3]), whereas the response to placebo was similar (9.5% vs. 7.5%; p = 0.05).[71]

Cicatrization was 8%, favoring 40 mg of esomeprazole over 20 mg of omeprazole (RR 1.08). Compared with other PPIs, esomeprazole was superior to omeprazole[72] (Table 2). In another randomized clinical trial (n = 2,425 EE *H. pylori* (−) - serology), the rate was also superior (esomeprazole 93.7% vs. omeprazole 84.2%, p = 0.001).[73]

The authors of a meta-analysis reported that esomeprazole increased the probability of cicatrization by 5% (RR 1.05; n = 15,316; absolute risk reduction 4%; and NNT 25). In grade A esophagitis, the NNT was 50, in grade B 33, in grade C 14, and in grade D 8. Improvement in heartburn (4 weeks) was 8% (RR 1.08). Despite its greater effectiveness, the size of the effect was modest, limited to the severity (C or D), and with no differences for heartburn.[74]

PPI response differs between phenotypes if the diagnosis is based on functional tests (pH (+) 0.73 versus pH (−) 0.72) or on GERD symptoms (50.5%). Response was greater in erosive esophagitis (57%), compared with NERD (49%) or non-GERD (35%).[75]

Symptom persistence despite the PPI

There are differences between the standard dose or double dose, with fluctuations (10-81%) in the %t pH < 4 (gastric) but not in the mean esophageal pH (p = 0.0001) between PPIs.[65,75,76]

Between 35 and 42% of the cases of NERD have normal esophageal acid exposure (EAE), complicating the response predictions due to their heterogeneity and refractoriness.[64,75–77] The latter can be explained because the diagnosis is based on symptoms, the persistence of weakly acidic reflux events extends to the proximal esophagus, and due to visceral hypersensitivity.[78]

The symptom index (SI) is the correlation of the heartburn events with the acid reflux episodes and can identify two subtypes in patients with normal acid exposure: reflux hypersensitivity (SI > 50%), and functional heartburn (SI < 50%).[79,80]

Reflux composition, EAE sensitization, and slow bolus clearance play a role in the perception of heartburn. ''Acid vapor'' can be perceived as heartburn and regurgitation,[73] and is greater if gas is in the refluxate, even without EAE.[81,82]

Twenty-four-h MII-pH monitoring defines PPI refractoriness with more specificity.[83,84] Symptoms can be produced at a pH > 4, 5, or 6. Failure can be due to poor disease classification. Approximately 20% (15-27%) of patients do not respond to the standard dose, even with adequate diagnosis.[80]

The Johnson-DeMeester criteria (%t pH < 4 for > 4.2% of the time) give the same weight to solutions with pH4 and pH1 (1,000-fold difference) but have low sensitivity for detecting short periods of high acidity (pH < 2) associated with symptoms.[85]

Visceral hypersensitivity is the primary mechanism responsible for non-cardiac chest pain (NCCP), functional alterations, refractory GERD, and reflux hypersensitivity.[86,87] Pain is induced by mechanical distension, acid, temperature, and osmolarity.[88–90] Chronic EAE(+) increases tissue permeability with the passage of sensitizing molecules of sensory afferent nerve endings.[90,91]

Extraesophageal manifestations and GERD

The therapeutic gain of a PPI over placebo is low (17%) in regurgitation[92,93] and in atypical symptoms (NCCP, pulmonary, laryngeal). In NCCP, response to a PPI increases when there is acid reflux (EAE [+] 56-85% vs. EAE [-] 0-17%).[94,95] The therapeutic trial has 84% sensitivity and 74% specificity for predicting reflux (excluding heart disease).[96,97]

It is difficult to establish the causal association in extraesophageal manifestations. The diagnostic accuracy of 24-h pH monitoring is low, whereas 24-h multichannel intraluminal impedance-pH (24-h MII-pH) aids in evaluating physical and chemical reflux composition.[98–100] Heartburn/regurgitation is absent in 40-60% of cases of asthma, 57-94% cases of laryngitis, 43-75% cases of chronic cough.[101]

Laryngitis due to reflux or laryngopharyngeal reflux

GERD is a cause of laryngeal inflammation that can produce hoarseness, dysphonia, odynophagia, throat clearing, chronic cough, globus, dysphagia, postnasal drip, and laryngeal spasm.[101,102] PPI response is similar to that of placebo in non-acid reflux,[103,104] with minimum therapeutic gain (0.04%).[103] Other authors have reported the superiority of PPIs (93 vs. 29%).[105,106]

Chronic cough due to reflux

It is diurnal, occurs in the vertical position, during speaking, when getting out of bed, and is food-related. There is

Table 2 Differences in relative risk at 4 and 8 weeks between PPIs versus 20 mg of omeprazole.

PPI versus 20 mg of omeprazole	Treatment duration	
	4 weeks	8 weeks
Esomeprazole (40 mg)	1.14(95%CI: 1.10, 1.18)	1.08(95%CI: 1.05, 1.10)
Lansoprazole (30 mg)	1.02(95%CI: 0.97, 1.08)	1.01(95%CI: 0.97, 1.05)
Pantoprazole (40 mg)	1.00(95%CI: 0.94, 1.07)	1.00(95%CI: 0.96, 1.04)
Rabeprazole (20 mg)	0.93(95%CI: 0.84, 1.03)	0.93(95%CI: 0.86, 1.01)
Lansoprazole, pantoprazole, rabeprazole	1.00(95%CI: 0.97, 1.04)	1.00(95%CI: 0.97, 1.03)

Source: Richter et al.[72]

no definitive diagnostic test. Twenty-four-h pH monitoring has 66% specificity.[107] Improvement and symptom resolution with PPIs are rare.[108]

Asthma due to reflux

Nighttime symptoms and functional parameters (pulmonary) respond better to PPIs in patients with heartburn and mucosal damage.[106] PPI use is not recommended in poorly controlled asthmatics, unless they present with symptoms of GERD. [107]

Clinical response to PPIs

Maintenance to prevent recurrence

PPI use (long-term) reduces recurrence[108,109] and is superior to placebo (93% vs. 29%).[110,111]

PPIs and overall clinical response

The overall effect in cicatrization over placebo was 11.4 (95% CI: 8.17-16.3) and in symptom improvement over placebo was 4.2 (95% CI: 3.25-5.48). Table 3 summarizes the data.[112]

Nocturnal acid breakthrough

Nocturnal acid breakthrough is a class effect seen with all delayed-release PPIs. Of PPI users (twice a day), ~ 70% have a nocturnal drop (10:00 pm-6:00 am) in gastric pH < 4 (> 1 continuous h).[113,114] With only a single morning dose, nocturnal acid breakthrough begins earlier than with evening dosing schedules, around 11:00 pm.[115]

Dose, isomerism, and mechanisms for greater performance

Split dose versus increased dose

The suppressive effect of a diurnal dose of esomeprazole was superior to other PPIs.[115] The split dose (20-20 mg) produced better control of pH (pH esomeprazole 3.9 ± 1.3 vs. pantoprazole 5.1 ± 0.9; p = 0.05) and NAB (pH esomeprazole 5.1 ± 0.9 vs. pantoprazol 3.9 ± 1.3; p = 0.05; %t pH > 4 pantoprazole 48.9 ± 22.8 vs. esomeprazole 68.1±19.7; p= 0.05).[116]

The increased dose (40-40 mg) of esomeprazole was more effective than pantoprazole for intragastric 24-h pH control (6.4 vs. 5.1; p < 0.00005), effect duration (21.1 h vs. 16.8 h; p < 0.0001), pH > 4 / 24 h (96.7% vs. 56.7%; p = 0.0002), and nocturnal acid control (85.4% vs. 63.6%; p = 0.0001).[117]

Another study reported that the effect was dose-dependent (40-40 mg 19.2 h [80.1%], 20-20 mg 17.5 h [73%] vs. 40 mg 14.2 h [59.2%]) with better control of the nocturnal %t pH > 4 (83.7% vs. 79.2% vs. 57.9%).[118]

Isomerism, carriers, and release mechanisms

Esomeprazole

The longer duration of the acid suppression effect with 40 mg of esomeprazole (14 h), compared with 20 mg omeprazole (12.1 h), 30 mg of lansoprazole (11.8 h), 20 mg of rabeprazole (11.5 h), and 40 mg of pantoprazole (10.0 h) has been related to isomerism,[119] but the additive effect of the magnesium carrier was not evaluated.

Pantoprazole magnesium

Magnesium increases the bioavailability of pantoprazole. At bioequivalent doses, esomeprazole vs. pantoprazole, both with magnesium, showed similar cicatrization rates (81% vs. 79%, p = NS). However, symptom relief was superior with pantoprazole-Mg (91.6% vs. 86.0%, p = 0.037).[120] Symptom severity decreased by 73% (intention to treat or ITT) and 80% (per protocol analysis).[121] In Mexican patients, nighttime GERD symptoms (42.7%) had a higher probability of being reflux-related extraesophageal symptoms (p < 0.001), which responded satisfactorily to pantoprazole-Mg.[122]

S-pantoprazole

Pantoprazole is a racemic mixture of S(+) and R(+)-pantoprazole. The S-isomer reduces the variation (metabolism), has predictable pharmacokinetics, is more effective, and is less dependent on cytochrome p450 2C19.[123] S-pantoprazole is more potent (1.5-1.9 times) and effective (3-4 times) than the racemate.[124] The use of low doses of S-pantoprazole was equally as effective as 40 mg of R(+)-pantoprazole in cicatrization (p = 1) and achieved better symptom control.[125] Another study reported similar healing rates (94% vs. 97%) between S-pantoprazole and R-pantoprazole.[126] Nevertheless, there are no randomized clinical trials that compare S-pantoprazole with second or third generation modified PPIs in the entire clinical spectrum of GERD.

Table 3 PPI compared with placebo, odds ratio (95% CI) for esophagitis cure.

PPI dose mg/day	Omeprazole	Pantoprazole	Rabeprazole	Lansoprazole	Esomeprazole
10	-	-	9.6(5.63,14.62)	-	-
15	-	-	-	8.23(4.87,12.8)	-
20	10.2(6.93,14.5)	6.88(4.23,10.8)	12.0 (7.78,18)	-	11.7(7.33,17.7)
40	14.9 (9.5,23.1)	11.6(8.16,16.1)	15.1(9.58,23.5)	-	15.5(10.2,22.0)
30	-	-	-	12.3 (8.6,17.0)	-
60	-	-	-	14.1(9.44,21.1)	-

Source: Zhang et al.[111]

Dexlansoprazole

The R-enantiomer of lansoprazole, dexlansoprazole modified release (DMR), utilizes a dual delayed release mechanism that increases the AUC_{24}. It makes up > 80% of the circulating lansoprazole after oral administration, has better clearance, and greater systemic exposure (> 5 times).[127,128] The capsule has two types of granules, 25% of which are released in the proximal duodenum (pH 5.5) and 75% in the ileum (pH 6.8), showing a double-peak profile (concentration/time).[129,130]

Moderate-to-severe esophagitis presents in 25-30% of all cases of esophagitis. A subgroup (10-15%) remains symptomatic and/or has mucosal damage (C and D) despite the PPI and > 40% of patients with NERD have treatment dissatisfaction.[131–133]

DMR was superior to lansoprazole in healing (60 mg: 86% vs. 79% and 90 mg: 90% vs. 85%, $p < 0.05$), with greater performance for 90 mg (8% gain). The NNT to prevent failure was 17 in grades C and D and 13 for all grades. DMR was efficacious in symptom control (> 80% heartburn resolution).[126]

Doses of 30 mg and 60 mg of DMR were superior to placebo (75% vs. 83% vs. 27%, $p < 0.0025$), with more diurnal heartburn-free days (91-96%) and nocturnal heartburn-free days (96-99%).[133] A clinical trial reported greater effectiveness with 90 mg (87%), compared with 60 mg (82%) or placebo (26%). The percentage of heartburn-free days was better with DMR (60 mg of DMR 97%, 90 mg 98%, and placebo 50%).[134] The indirect comparisons in cicatrization with 40 mg of esomeprazole were not significant.[135]

In relation to diurnal heartburn (50.0% vs. 54.9% vs. 17%; $p < 0.00001$) and the percentage of nights with no heartburn (80.8% vs. 76.9% vs. 51.7%, $p > 0.00001$), DMR (30 and 60 mg) was superior to placebo.[136] DMR at 30 mg was more effective than esomeprazole at 20/40 mg (RR: 2.01 vs. 2.17) in cases of heartburn [137] and 30 mg of DMR was more effective (80%) in patients in whom previous use of other PPIs had failed.[138]

Nighttime GERD symptoms are associated with poor sleep quality. Up to 50% of patients complain of nocturnal symptoms.[139,140] Frequency was reported at 42.7% in 4,302 Mexican patients with GERD. [141]

The dose of 30 mg of DMR was more effective than placebo for heartburn control (73.1% vs. 35.7%, $p < 0.0001$), improving sleep quality (69.7% vs. 47.9%; $p < 0.001$), work productivity, and for reducing the severity of nocturnal symptoms (69.7% vs. 47.9%; $p < 0.001$).[142]

Ilaprazole

Ilaprazole is a derivative of benzimidazole metabolized by CYP3A4 with a t1/2 of 8.1-10.1 h. It is a third generation prodrug.[30,143] The comparison between ilaprazole (5, 10, and 20 mg) versus 20 mg of omeprazole showed significant differences in the mean pH > 4 but not in the intragastric %t pH > 4.[144] Nevertheless, the effect was inferior to that previously reported in healthy volunteers.[145] The authors concluded that the population differences (Western versus Asian) could explain the results.

Clinical trials have focused on the non-superiority of other PPIs in relation to low doses of ilaprazole in cicatrization. The rates (per protocol analysis) for 40 mg of esomeprazole, 10 mg of ilaprazole, and 15 mg of ilaprazole were 93.3%, 94.9%, and 97.6% at 8 weeks ($p = 0.611$).[146] However, no Western clinical trials have been conducted with other PPIs on diurnal and nocturnal acid secretion control, extraesophageal manifestations, chest pain, or refractory PPI cases.

Tenatoprazole

The prodrug, tenatoprazole (pKa = 4.04), is an imidazopyridine (non-benzimidazole) bound to a pyridine ring (methylsulfinyl) that is bound to Cys813 and Cys822. It has a prolonged t1/2 (8.7 h). The AUC of 40 mg of tenatoprazole is longer than that of 40 mg of esomeprazole, and thus controls nocturnal acid secretion better (pH > 4: 4.6 versus 4.2).[147,148] Said PPI has yet to be placed on the market.

The new knights on the horizon

A new class of drugs targeted at gastric acid suppression has been discovered: potassium pump blockers, K+ of the ATPase (P-CABs). They impede the exchange of H+ with a high affinity for K+ (E2 conformation). An important advantage of that pharmacologic focus is the rapid onset of the effect, with complete inhibition of gastric acid secretion within 30 min of drug administration.

Vonoprazan achieves rapid and more prolonged acid suppression, compared with PPIs.[149] Mean intragastric pH (day 7) in healthy subjects that received 10-40 mg (once a day) of vonoprazan in a Japanese and Western population had a linear response. Response was greater with a dose of 40 mg, reaching a pH > 4/24 h in a percentage of 86.5 ± 15.5 of the subjects (day 1) and 100 ± 0.1 (day 7).[149]

The next step is to evaluate the usefulness and clinical benefit of extreme acid suppression, as well as the long-term adverse events. In addition, the size of the effect in randomized clinical trials must be analyzed upon comparing the P-CAPs with PPIs, with respect to the broad spectrum of GERD.

The search for the grail continues.

Conclusions

PPIs have shown their effectiveness, safety, and tolerance in the spectrum of GERD. Clinical response is associated with their pharmacokinetic properties. PPI optimization is based on dose modifications (split or increased), galenic formulations, isomerism, and mechanisms of release. Efforts have been directed at increasing the half-life, maximum concentration, and area under the curve of the plasma concentrations. Even though a favorable symptom response in acid-related diseases is to be expected, pharmacologic performance yield is greater in patients with abnormal esophageal acid exposure (EAE) confirmed through functional tests. Thus, the clinical behavior of true NERD (absence of mucosal damage with positive EAE) is similar to that of erosive esophagitis.

The size of effect of the adverse events associated with PPIs is situated in the area of potential risk for methodological bias, given that their results have been based on observational studies that have a higher risk for confounding factors.

Basic pharmacokinetic knowledge and understanding of the disease enables the optimization of a PPI in clinical

practice. The race for acid suppression depends on the entity within the clinical spectrum of GERD.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study. The present study is a review of the literature in English and Spanish to find evidence on the efficacy, safety, tolerance, and adverse events of a class of drugs.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article. 53-18AR)

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Conflict of interest

Sergio Sobrino-Cossío, Oscar Teramoto-Matsubara, Gualberto Mateos-Pérez, Juan Miguel Abdo-Francis, Antonio Orozco y José Tawil have been lecturers for Laboratorios Takeda, Mexico.

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