

POINT OF VIEW

Proton pump inhibitors in gastroesophageal reflux disease: “a custom-tailored therapeutic regimen”

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ABSTRACT

The Montreal Definition and Classification divides Gastroesophageal Reflux Disease (GERD) into esophageal symptomatic syndromes (and with mucosal damage) and extraesophageal syndromes (with acid established association and proposed association). In typical GERD symptoms, an 8-week treatment with PPIs is satisfactory in most cases (> 90%). Response rates to PPIs in GERD are highly variable, as they also rely on an appropriate clinical diagnosis of the disease; endoscopy differentiates the macroscopic GERD phenotype. The non-erosive variety (50-70% prevalence) has a different symptomatic response rate, as gastric acid is not the sole etiology of symptoms. The possible explanations of treatment failure include treatment adherence, PPI metabolism alterations and characteristics, and inadequate diagnosis. Refractory symptoms are related to gastric content neutralization by the chronic use of PPIs.

Extraesophageal manifestations are associated with other pathophysiological mechanisms where an autonomic nervous system disturbance gives rise to symptoms. In these clinical entities, the relationship between symptoms and acid needs to be established in order to determine the use of PPIs, or consider other drugs. In other words, so as to “custom-tailor the best-fitting therapy” we need to answer the questions for whom, for what, how and for how long. Finally, PPI safety and tolerability are factors to be considered in elderly patients requiring chronic PPI use, who usually have chronic concomitant illnesses.

Key words: GERD. Heartburn (pyrosis). Non-erosive GERD. PPIs. GERD extraesophageal manifestations.

INTRODUCTION

To custom-tailor a therapeutic regimen is to give each disease entity a treatment created *ad hoc* for the relief of its manifestations. The pathophysiology, diagnosis and treatment of the formerly known as acid-peptic disease have changed significantly in the last years. This is owing to proton pump inhibitors (PPIs) and the technological breakthrough in diagnostic procedures. In the past, acid-peptic disease was addressed as a single clinical entity enclosing many conditions that have now been better defined. There is a therapeutic proposal for each clinical entity that achieves symptom relief in most cases; however, there are some refractory or recurring cases for which the existing therapeutic tools need to be suited.

In gastroesophageal reflux disease (GERD), response rates to PPIs are variable and rely on the clinical diagnosis –manifestations, comorbidity, and symptom overlap with other highly prevalent clinical entities such as the gastrointestinal functional disorders (FGD)–. Patients with typical symptoms and esophageal erosions have a satisfactory (> 90%) response rate to PPIs after 8 weeks, in most cases, and even in the short term. However, when symptoms are persistent or recurring, response rate is related to the phenotype of the patient’s

Received: 16-02-2012

Accepted: 28-06-2012

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Sobrino-Cossío S, López-Alvarenga JC, Remes-Troche JM, Galvis García ES, Soto-Pérez JC, Teramoto-Matsubara O, Morales-Arámbula M, Orozco-Gamiz A, Tamayo-de-la-Cuesta JL, Mateos G, Jiménez A, Saez A y Vargas JA. Proton pump inhibitors in gastroesophageal reflux disease: “a custom-tailored therapeutic regimen”. *Rev Esp Enferm Dig* 2012;104:367-378.

predominant clinical syndrome (1). Endoscopy differentiates the macroscopic GERD phenotype; however, in the non-erosive variety (50-70% prevalence) symptomatic response rates differ significantly among groups, as gastric acid is not the sole etiology. Treatment failures are related to treatment adherence (insufficient time, inadequate dose, time relationship between drug and food intake), alterations in drug metabolism (delayed gastric emptying, rapid metabolizers), PPI characteristics (efficacy, safety, tolerability and pharmacogenomics) and an inadequate diagnosis (eosinophilic esophagitis, gastroparesis, functional dyspepsia) resulting from symptom overlap. Refractory symptoms (associated to weakly acidic and non-acidic reflux) are related to neutralization by the chronic use of PPIs (1-3).

Extraesophageal manifestations may be associated with other pathophysiological mechanisms where an autonomic nervous system disturbance gives rise to symptoms. In these clinical entities, the relationship between symptoms and acid needs to be established in order to predict the clinical response to PPIs with greater certainty, or consider other drugs. In other words, so as to “custom-tailor the best-fitting therapy”, we need to answer the questions for whom, for what, how and for how long, taking into consideration other highly prevalent symptomatic entities. Finally, PPI safety and tolerability are factors to be considered in elderly patients requiring chronic PPI use, who usually have chronic concomitant illnesses.

PROTON PUMP INHIBITORS (PPIs)

PPIs, benzimidazole and imidazopyridine derivatives, changed the natural history of acid-related disorders –peptic ulcer (PU), erosive gastropathy and GERD)–. They have superior therapeutic efficacy and clinical effectiveness than histamine type 2 receptor antagonists (H2RAs) to suppress

acid secretion in a sustained manner (4). Omeprazole was the first drug of this pharmacological class (1989); lansoprazole (1995), rabeprazole (1999), pantoprazole (2000) and esomeprazole (2001) were subsequently introduced in the market. The annual direct and indirect cost of treating GERD in the U.S. exceeds 10 billion dollars (4). However, PPI response rate over time is far from being optimal (4), and the adverse event incidence has increased from 30,000 in 1998 to 90,000 in 2005 (4,5).

How to choose a PPI?

While all of them are effective, studies show variable rates in intragastric pH control and symptomatic response. The decision of choosing a PPI should be based on efficacy, safety, tolerability, quality of life, pharmacogenomics and cost-effectiveness. Ordinal Likert scales measure PPI impact on symptom control.

The ideal PPI characteristics should include dose-response, diverse galenic formulations, similar oral and intravenous dose, lineal pharmacokinetics, precise pharmacodynamics, no drug interactions, safety and good tolerability, a cost-benefit or cost-usefulness analysis that favors the patient, at least 80% efficacy in immediate and sustained symptom relief, and in addition, they should avoid complications or relapses (Table I). However, there are several factors that affect drug efficacy, among them: the time relationship between drug and food intake, which produces changes in bioavailability, half-life ($t_{1/2}$), area under curve (AUC_{0-24}); cysteine binding (6); galenic formulation; dosage (standard, split or double); tolerability; adverse events (interaction with cytochrome P₄₅₀, CYP2C19 and CYP3A4) and side effects. Clinical effectiveness may be approximately estimated by multiplying the drug efficacy, diagnosis effectiveness and treatment

Table I. Pharmacokinetic properties of PPIs (oral)

	<i>Omeprazole</i>	<i>Esomeprazole</i>	<i>Lansoprazole</i>	<i>Rabeprazole</i>	<i>Pantoprazole</i>
Bioavailability (%)	30-40	50-68	80-85	52	77
Time to maximum plasma concentration (h)	0.5-3.5	1.0-2.0	1.5-2.0	1.0-2.0	1.1-3.1
Plasma elimination half-life (h)	0.5-1.0	11.3	1.3-1.7	0.7-1.5	1.0-1.9
Plasma kinetics	Non-linear	Non-linear	Linear	Linear	Linear
Protein binding (%)	95	97	97	96	98
Metabolism	Hepatic (CYP2C19, CYP3A4)	Hepatic (CYP2C19, CYP3A4)	Hepatic (CYP2C19, CYP3A4)	Non-enzymatic reduction, Hepatic (CYP2C19, CYP3A4)	Hepatic (CYP2C19, CYP3A4)
Urinary excretion of oral dose (%)	77	80	14-23	30-35	71-80

adherence (7). For example, even if drug efficacy and diagnosis effectiveness are good (90%), a decreased treatment adherence, from 90 to 70%, will negatively impact treatment response rate.

Mechanism of action of PPIs

The human stomach contains over a billion parietal cells secreting 0.16 M hydrochloric acid (HCl) in response to three physiological stimuli: acetylcholine, histamine and gastrin. The proton pump (PP) of parietal cells is responsible for gastric acid secretion, which is carried out in three phases: 1) cephalic, 2) gastric, and 3) intestinal, accounting for 30, 50 and 20%, respectively (8). These physiological particulars explain why these drugs are recommended to be taken 30 minutes before meals, so as to maximize proton pump inactivation (30% + 50% = 80%) and thus optimize their performance, since it is essential to bear in mind that the $t_{1/2}$ of PPIs is very short (0.7-1.2 hours).

Pharmacokinetic and pharmacodynamic differences can be observed among the different PPIs, which might influence their clinical application. However, the genotype or drug interactions may cause a same PPI to have widely different therapeutic effects on individuals (7,9). PPIs are prodrugs; they are inactive weak bases with a neutral charge (lipophilic) that pass through the stomach intact and are absorbed in the duodenum. They reach the bloodstream (plasma concentration \approx 0.5 to 2 mg/ml), bind to proteins (> 95%), cross the parietal cell membrane and selectively accumulate in the acidic canaliculi of the parietal cell basolateral membrane (organ specificity). In the body, the parietal cell is the only membrane-enclosed space with a pH < 4; rabeprazole can also accumulate in other compartments with a pH > 4 (neuron, kidney and bone). PPI selective activation is induced by a first protonation of the pyridine moiety at a pKa1 value ranging from 3.8-4.5, which renders them less permeable and increases their accumulation. A second protonation, pKa2 (benzimidazole or imidazopyridine moiety), on the acidic surface or in the acid compartment of the proton pump effects a chemical rearrangement producing an active metabolite (sulfenic acid) which inhibits the H⁺,K⁺ ATPase enzyme. The pKa2 determines the activation rate of PPIs and affects the stability of acid suppression. The active form of the drug forms covalent disulphide bonds with cysteines accessible from the exoplasmic surface of the enzyme thus inhibiting it; studies by Sachs et al. showed that proton pump inhibition is not irreversible (9-14).

What does reversibility of PPI binding to proton pumps depend on?

After inhibition by PPIs, recovery of gastric acid secretion depends on two factors (8,9,14): a) protein turnover (synthesis of new proton pumps) which is determined by

the enzyme half-life ($t_{1/2}$) (\approx 54 hours); and b) reversal of the disulphide bonds. The half-time of recovery of gastric acid secretion in rats following inhibition by omeprazole is 15 hours; in humans it is 28 and 46 hours with omeprazole and pantoprazole, respectively (6,10-14). The PPI binding pattern to cysteine (sixth transmembrane domain –TM6–) is what makes PP inhibition reversible or not; omeprazole and esomeprazole bind to cysteines 813 and 892, while lansoprazole and rabeprazole bind to cysteine 813, 892 and 321. Up to 84% of omeprazole binds to cysteine 813, whereas 50% of pantoprazole and tenatoprazole binds to cysteine 813 and the other 50% to cysteine 822. Glutathione, an antioxidant that protects cells from reactive oxygen species (free radicals and peroxides), cleaves disulphide bonds with cysteine 813, which is located more superficially in the membrane. On the other hand, cysteine 822 is located deep within the TM6 which makes it inaccessible to glutathione, thus rendering inhibition of gastric acid secretion more stable and less reversible (9-14). Plasma $t_{1/2}$ of tenatoprazole is more prolonged than that of omeprazole, lansoprazole, pantoprazole, rabeprazole and esomeprazole (8 *versus* 1-1.5 hours); therefore, its antisecretory effect last longer (13).

Variations in the crystal structure and hydrophobic nature result in an increased bioavailability of the sodium form of PPIs when compared to the free form (14). PPIs differ in their behavior due to their bioavailability (77% for pantoprazole, 80-90% for lansoprazole, and 89% for esomeprazole), concentrations –maximum (C_{max}) and minimum (C_{min})–, AUC_{0-24} , and elimination pathways. PPIs are subject to hepatic metabolism by isoenzymes of the CYP system [primarily CYP2C19 (S-mephenytoin-hydroxylase) and CYP3A4 (except rabeprazole)] that transform them into inactive molecules prior to their elimination (6,12-14).

Metabolism of PPIs

There are some differences among PPIs that result from their degradation by the cytochrome P₄₅₀ (CYP) system. Omeprazole is metabolized to 5'-OH-omeprazole (by CYP2C19) and 5'-OH-omeprazole sulfone (by CYP3A4). Esomeprazole, with a similar metabolism, has a slower hydroxylation rate. They both inhibit the activity of CYP2C19, a phenomenon that increases their plasma concentration and explain the drug interactions, particularly with clopidogrel, which as a prodrug does not reach activation because of CYP2C19 inhibition. Lansoprazole is metabolized to 5'-OH-lansoprazole and lansoprazole sulfone (by CYP2C19 and CYP3A4). Pantoprazole is metabolized to 5'-OH-pantoprazole and pantoprazole sulfone (by CYP2C19 and CYP3A4), and subsequently to pantoprazole sulfate by a sulfotransferase, thereby minimizing drug interactions. The metabolic pathway of rabeprazole is non-enzymatic reduction to a thioester compound; only a small part is oxidized to demethylated rabeprazole or rabeprazole sulfone via CYP2C19 and CYP3A4 (9).

Genetic polymorphisms (GPMs) of CYP isoenzymes (CYP2C19)

GPMs can explain the interindividual and interethnic variability in the pharmacokinetics of PPIs. The CYP2C19 protein (490 aminoacids) is encoded by the CYP2C19 gene (9 exons; chromosome 10; 10q24.1-q24.3). GPMs occur in Japanese (15-22.5%), Chinese (13-20%) and individuals from Melanesia (70%). CYP2C19*1 represents a wild-type allele (15). In poor or slow metabolizers (SMs), two alleles –CYP2C19*2, almost exclusively in Caucasians (a point mutation defect in exon 5; base change from guanine to adenine) and CYP2C19*3 in Asians (premature stop codon at position 636 of exon 4; base change from guanine to adenine)– produce a truncated protein and inactive isoenzyme. Three groups of GPMs can be identified depending on the genotype: enzyme activity is increased (enzyme *1/*1) in rapid metabolizers (RMs), it is moderate (enzyme *1/*2 and *1/*3) in intermediate metabolizers (IMs) and reduced (enzyme *2/*2, *2/*3 and *3/*3) in slow metabolizers (SMs). The prevalence of SMs is 2.3-8.5% in the European population, and 8-23% in China and Japan, in whom plasma ([p]) PPI concentrations are increased. Recently, a new variant allele was described (CYP2C19*17 allele, -806 C>T and -3402C>T), which is responsible for ultrarapid metabolism and is more prevalent in the Swedish population than in the Chinese (18 *versus* 4%). The AUC₀₋₂₄ value for an oral omeprazole 20 mg dose in individuals who are homozygous for the CYP2C19*17 allele reached only 63% of that in CYP2C19*1 homozygotes. In December 2004, a CYP2C19 genotyping test (AmpliChip®CYP450) became commercially available (by Roche Diagnostics) which has a 99% efficacy in detecting known GPMs of CYP2D6 y CYP2C19 (9).

Clinical relevance of CYP2C19 polymorphisms

Pharmacokinetic and pharmacodynamic differences are reflected in PPI antisecretory effects with a vast interindividual variability. SMs show low clearance and high plasma concentrations of PPIs, they experience strong acid suppression and enhanced therapeutic effectiveness. On the contrary, RMs show increased clearance, low plasma concentrations and decreased antisecretory effect. The differences among PPIs are reflected in the different AUC₀₋₂₄ values. The AUC₀₋₂₄ values of omeprazole and lansoprazole are 4- to 15-fold higher in SMs, and 2- to 3-fold higher in IMs. Pantoprazole shows a similar behavior; its AUC₀₋₂₄ values are 6-fold higher in SMs. The AUC₀₋₂₄ ratio between SMs and RMs with rabeprazole is 1.2, owing to its different metabolism, as its AUC₀₋₂₄ values are not affected by CYP2C19 genetic polymorphisms. Esomeprazole has higher metabolic stability and higher bioavailability due to its CYP2C19 inhibitory effect, resulting in an increased AUC₀₋₂₄, irrespective of the genotype (9).

How can the action of PPIs be modified?

Pharmacologically, there are a number of approaches that can improve the action of PPIs. One way is to prolong the elimination t_{1/2}. After oral intake (15-60 min before a meal) of lansoprazole 30 mg, rabeprazole 20 mg, pantoprazole 40 mg, omeprazole 40 mg or esomeprazole 40 mg, plasma concentrations decline by the end of the day (dosing interval). Although PPIs do not achieve pharmacokinetic steady-state at conventional dosing, they do achieve pharmacodynamic steady-state. The first dose inhibits ≈ 70% of the active proton pumps; the balance between proton pump inhibition by disulphide bonds and the synthesis of new proton pumps is reached by the third day, when steady-state inhibition of gastric acid secretion is achieved (16,17). Extending plasma t_{1/2}, will progressively prolong the antisecretory effect. Reducing individual variability in pharmacokinetics and pharmacodynamics will result in a more rapid onset of action and sustained acid suppression, and if absorption is independent of meals, it will translate into better efficiency (18). The antisecretory effect can be predicted by pharmacokinetic parameters –(AUC₀₋₂₄ and percentage of time with intragastric pH > 4 (% t pH > 4))–. The longer the plasma t_{1/2} is, the higher the AUC₀₋₂₄ value, and hence the antisecretory effect. Maintenance of intragastric pH > 3 is correlated to healing of duodenal ulcer, of intragastric pH > 4 to healing of gastric ulcer, and of intraesophageal pH > 4 to healing of erosive esophagitis (19-21). Lansoprazole, pantoprazole and rabeprazole have linear pharmacokinetics (correlation between C_{max} and AUC₀₋₂₄), unlike omeprazole and esomeprazole (non-linear), which significantly inhibit CYP2C19 (22).

The imidazopyridine ring is responsible for the slower activation of pantoprazole and tenatoprazole. The trifluoromethyl group addition to the benzimidazole moiety of pantoprazole prolongs its plasma t_{1/2}, thereby stabilizing the molecule (23). Pantoprazole has a constant absolute bioavailability (77%), with extensive serum protein binding (98%) and minimal CYP-mediated drug interactions; its absorption is not affected by food intake and it has no active metabolites. Tenatoprazole has theoretical advantages over benzimidazole PPIs in acid control, particularly in nighttime GERD (24). Potassium-competitive acid blockers (P-CABs), AZD0865, CS526, revaprazan and soraprazan, inhibit proton pumps and acid secretion irreversibly and much more quickly (within a half-hour) (25,26).

Another way of optimizing PPI performance is to double or split the PPI dose. A randomized clinical trial (CT) reported that esomeprazole 80 mg was more effective than lansoprazole 60 mg in maintaining intragastric pH > 4 for > 16 h; the split dose of omeprazole was more effective than the standard dose in maintaining pH control (29). No differences in daytime pH control were observed with different omeprazole dosing regimens (40-0-0, 0-0-40 mg *versus* 20-0-20 mg) during 7 days (n = 18 healthy subjects); the split dose was superior in controlling nighttime intragastric

pH than the standard dose given in the morning or in the night (60 vs. 30 vs. 20%; $p = 0,02$) (28).

An additional effective tool is to modify PPI release systems for a sustained action, by making them dual or multiple so that the active substance, irrespective of the dose, is available for absorption for an extended period of time. The physicochemical properties and biological conditions of the individual allow for maximal therapeutic benefits.

The different release mechanisms used by PPIs are (29,30):

- *Conventional or immediate*: traditional form that delays transiently the antisecretory effects.
- *Extended*: slow form that extends the dosing interval.
- *Modified*: the sodium form carriers allow a faster absorption with high C_{max} ; the magnesium form, with a slower absorption, increases terminal $t_{1/2}$. Programmed release increases PPI bioavailability.
- *Controlled*: (predetermined kinetic pattern) it releases the active substance while decreasing side effects; prolongs the period of time, and protects the drug (from enzyme or acid degradation).
- *Prolonged*: it includes substances that regulate drug absorption or elimination, thereby extending the therapeutic effect (maximum efficacy), and preventing drug biodegradation during distribution with minimal risks. The active substance is released in a specific site of the body (vectors and/or carriers) at a predetermined rate and period of time.
- *Repeated*: fractions are released at specified time intervals; the first, as soon as the drug is administered, and the other, in a scheduled fashion.
- *Delayed*: this form is supplied as encapsulated enteric-coated granules (omeprazole and lansoprazole hard gelatin capsules) or enteric-coated tablets (pantoprazole tablets, rabeprazole tablets and omeprazole mups –multiple unit pellet system).
- *Sustained*: modified extended release form; the first dose is released rapidly, and then gradually. An ideal system should release the drug at a constant rate during the whole dosing interval. Ideal specifications are: short $t_{1/2}$ without first-pass metabolism, narrow therapeutic index and efficient absorption (31).

Immediate-release omeprazole (IR-OME + 1680 mg of sodium bicarbonate NaHCO_3 , equivalent to 460 mg of sodium) has a faster onset of action, although different pharmacokinetics and pharmacodynamics, and its acid secretion inhibitory effect is similar to that of the delayed-release formulation. The higher bioavailability of IR-OME produces a prolonged suppression; alkalization (resulting from sodium bicarbonate) quickly activates the proton pumps, which are then inhibited by the drug. Nocturnal dosing of IR-OME is more effective than the standard dosing and similar to the split dosing of esomeprazole (20/20 mg) (32). The nocturnal 40 mg dose was more effective than pantoprazole 40 mg (nocturnal) during six days and the double dose (40-0-40 mg) during 7 days (the mean % of time that intragastric pH was > 4

was 55% vs. 27%, $p < 0,001$). However, control of daytime pH was similar to that of the delayed-release formulation (33-35).

AGN 201904-Z enteric-coated capsules (600 mg/day) were more effective than prolonged-release esomeprazole (40 mg/day) in maintaining nocturnal and 24-h pH > 4 for a longer period of time ($p = 0,0001$) (36).

The dual delayed-release mechanism of dexlansoprazole (lansoprazole enantiomer), which releases drug at 2 or 3 time points, prolongs the antisecretory effect. Its pharmacokinetic effects prior to food intake (either breakfast, lunch, dinner or a nighttime snack; normal dietary habits) were bioequivalent, with a similar plasma $t_{1/2}$ (1.27-1.44 h) and no significant differences in mean 24-h intragastric pH (37-40).

Rabeprazole sodium extended-release 50 mg capsules (rabeprazole-ER) use a multiple pulsatile release system. Even though acid suppression is similar to that of prolonged-release formulations, this mechanism extends the pharmacodynamic effect thus increasing plasma exposure (41).

Due to difficulties in achieving adequate symptom control, efforts have been made to optimize PPI efficiency and performance with the aim of increasing their bioavailability. Modifications have been made in the racemic structure (isomers) that improve the safety profile and decrease side effects and drug interactions. Also, the plasma $t_{1/2}$ has been extended in new drugs such as tenatoprazole (a PPI that is a racemic mixture of two stereoisomers) and P-CABs.

Clinical evidence

Studies in healthy volunteers about the effect of PPIs on GERD symptom control and mucosal healing show differences in efficacy, onset of action, potency, and duration of acid suppression (% of time during which intragastric pH > 4/24 h) (42-44). At standard doses, PPIs maintain intragastric pH > 4 for 10-14 hours (46); doubling the dose increases control, although 50% subjects will have a drop in nocturnal pH with its related symptoms (45). A pharmaco-economic analysis is required, however, to assess impact. Intragastric pH and acid secretion are predictors the acid load to the esophagus, but do not translate into the degree -abnormal acid exposure (AAE) in esophagus (46,47) (Table II).

In erosive esophagitis, the 8-week healing rates produced by acid suppressive therapy are related to the amount of time over a 24-h period that intragastric pH is maintained above 4. The percentage of time during which intragastric pH > 4 has been used as an important marker of the efficacy of PPIs. However, clinical trials show interindividual variability and require crossover randomized designs; the *Helicobacter pylori* status is to be reported, as infection by this bacterium increases intragastric pH as well as the time between drug and food intake (48-51); results cannot extrapolated to non-erosive GERD; and in addition, the type of pH electrodes and their position in the stomach are to be taken into account (Fig. 1).

Table II. Different clinical trials (CT) with PPIs and their effect on gastric acid suppression

Reference	Design	n	PPI and % time in which intragastric pH > 4.0				p
Lind et al., 2000	Randomized, double-blind, crossover CT	38	Eso 40 mg 69.8% Standard dose	Eso 20 mg 53.0%		Ome 20 mg 43.7%	0.01
Rohss et al., 2002	Randomized, open-label, crossover CT	130 0	Eso 40 mg 68.4% Standard dose			Ome 40 mg 62.0%	0.001
Wilder-Smith et al., 2003	Randomized, crossover CCT	24	Eso 40 mg 65% Standard dose			Lan 30 mg 53%	0.001
Miner et al., 2003	Randomized, crossover CCT	34	Eso 40 mg 58.4% Standard dose	Lan 30 mg 47%	Ome 20 mg 49.1%	Panto 40 mg 50.5%	Rabe 20 mg
Rohss et al., 2004	Randomize, open-label, crossover CCT	36	Eso 40 mg 57.5% Standard dose			Lan 30 mg 44.6%	0.0001
Rohss et al., 2004	Randomize, open-label, crossover CCT	38	Eso 40 mg 69.8% Standard dose			Eso 20 mg 53.0%	
Rohss et al., 2004	Randomize, open-label, crossover CCT	32	Eso 40 mg 67.1% Standard dose			Panto 40 mg 45%	0.001
Rohss et al., 2004	Randomize, open-label, crossover CCT	35	Eso 40 mg 59.6% Standard dose			Rabe 20 mg 44.6%	0.0001
Johnson et al., 2005	Randomize, open-label, crossover CCT	45	Eso 80 mg 81.3% Double dose	Lan 50 mg 65.4%	Eso 40 mg 60.1%	Lan 30 mg 51.3%	0.05

Recently, the management of extraesophageal manifestations associated with nighttime GERD has become relevant, for example, in a clinical trial with 4,302 Mexican GERD patients (53.9% female, 46.1% men) found a nocturnal GERD frequency of 42.7%, in contrast with the frequency reported in the survey with U.S. general population conducted by the Gallup Agency at the request of the AGA. In the Mexican study the symptoms were evaluated through ReQuest (specific questionnaire that assesses GERD symptoms) results obtained showed that symptoms intensity improved with pantoprazole 40 mg o.d treatment during 4 weeks, regardless of the predominance of daytime symptoms or night (54). Table III shows the data from an interim analysis (with 3,306 GERD patients) that was performed as part of this study. As seen, the improvement in each of the dimensions evaluated by ReQuest is about 50% after 7 days of treatment.

Empirical therapy with PPIs is pragmatic; the likelihood of having GERD is high in patients who respond to treatment. But it draws no distinctions between phenotypes, and it does not set aside those acid-related disorders that respond to PPIs or placebo; furthermore, a lack of response does not mean absence of disease (1). Patients with persistent symptoms who are treated with standard or double doses report variability (10 to 81%) in the percentage of time in which intragastric pH < 4; nevertheless, as little as 20% of time with esophageal pH < 4 is not normal and correlates with weakly acidic reflux episodes (53). These divergences could be resolved if the AUC₀₋₂₄ behavior is described with pH cut-off points (logarithmic scale) rather than the % of time in which pH < 4.

A Cochrane Review (48) of 134 controlled clinical trials (CCT) (n = 36,978) reported that PPIs are more effective than H2RAs and placebo in healing esophagitis, controlling

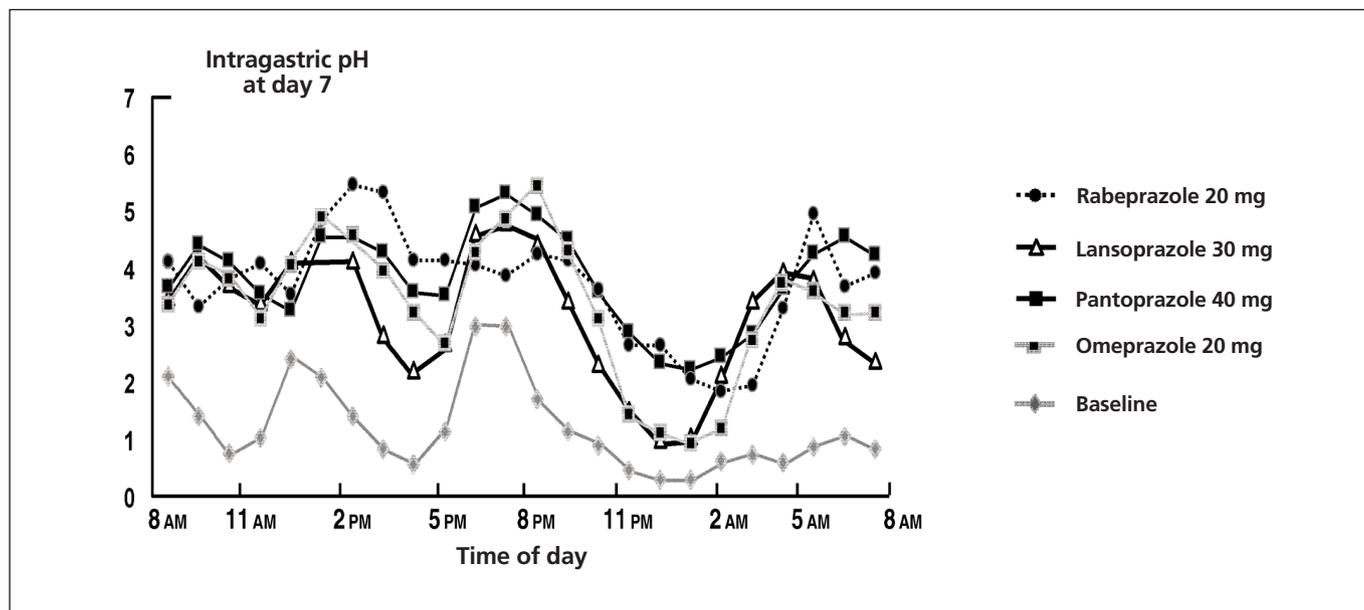


Fig. 1. Comparison of the intra-gastric pH profile of different PPIs. Mean 24-h intra-gastric pH with 4 PPIs versus baseline (49).

symptoms and decreasing the rate of recurrence, with no significant differences among them and a modest gain when doubling the dose (54,55). Table IV shows the percentages of intra-gastric pH control in different clinical trials (56,57).

PPIs are more efficacious than placebo in erosive esophagitis -55.5 (95%CI: 51.5-59.5) versus 9.5 (95%CI: 7.1-11.1-) and non-erosive esophagitis -36.7 (95%CI: 34.1-39.3) versus 7.5 (95%CI: 2.5-12.5)-. The therapeutic benefit is greater in patients with erosive disease -48% (95%CI: 24.6-93.8) versus 27.2% (95%CI: 20.9-35.3)- (53). Over 40% of symptoms are not induced by acid (54). There are divergences among the rate of mucosal healing (90%), symptom improvement (73-76%) and symptom resolution (31-38%) (55). Failure to control intra-gastric pH, especially during sleep, is related to a low rate of

symptomatic response in patients with extraesophageal manifestations (48). The failure mechanisms are poor treatment adherence, weakly acidic reflux (pH 4-7), visceral hypersensitivity (functional heartburn), duodenogastric reflux, delayed gastric emptying, eosinophilic esophagitis, and comorbidity (56).

Peptic esophagitis has been associated with dysphonia, chest pain and globus sensation; and with sinusitis, pharyngitis, aphonia, laryngeal stricture, chronic bronchitis, asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, bronchiectasia, pulmonary collapse and pneumonia (57,58). The extraesophageal reflux syndrome (asthma, laryngitis and cough) is more frequent in esophagitis and/or GERD symptoms (OR 1.2-3.0) (59). Our group assessed GERD symptom intensity (4-point Likert scale) in 2,171 women

Table III. Interim analysis: mean values for 6 dimensions ReQuest during 4 weeks of pantoprazole treatment. Improvement in dimensions (mean 77%; 74-80%) (54)

Days	Heartburn	Upper abdominal discomfort	Lower abdominal discomfort	Nausea	Sleep disturbance	Negative impact in the overall wellbeing
Baseline	6.25	5.96	4.67	3.91	4.29	6.23
2	5.38	5.13	4.09	3.33	3.67	5.48
3	4.51	4.33	3.5	2.74	3.07	4.66
4	3.8	3.66	3.01	2.33	2.64	3.98
5	3.23	3.13	2.63	2.05	2.35	3.42
6	2.87	2.77	2.38	1.83	2.12	3.03
7	2.53	2.48	2.18	1.68	1.96	2.4
14	1.99	1.98	1.76	1.36	1.63	2.14
21	1.56	1.57	1.45	1.13	1.37	1.72
28	1.24	1.29	1.22	0.95	1.13	1.36

Table IV. Four- and eight-week controlled clinical trials (CCTs) comparing esomeprazole versus other PPIs in the healing of reflux esophagitis (37)

Study	Dose	Esophagitis grade	n	ITT intention-to-treat					
				4 weeks		8 weeks		Healing	
				Yes	No	%	Number	%	Number
Castell, 2002	Lans 30	LA A-D	2,617	1,877	740	71.7	220	413	84.2
	Eso 40		2,624	1,987	637	75.7	4	326	87.6
Howden, 2002	Lans 30	2-4	143	107	36	74.8	127	16	88.8
	Eso 40		141	108	33	76.6	123	18	87.2
Fennerty, 2005	Lans 30	C-D	502	238	264	47.4	367	135	73.1
	Eso 40		499	278	221	55.7	386	121	77.4
Kahrilas, 2000	Ome 40	A-D	1,209	805	404	66.5	978	231	80.9
	Eso 40		654	465	189	71.1	573	81	81.4
Richter, 2001	Ome 40	A-D	1,209	805	404	66.5	978	231	80.9
	Eso 40		1,216	956	260	78.6	109	123	89.9
Gillesen, 2004	Panto 40	B-C	113	55	58	48.7	94	19	83.2
	Eso 40		114	68	46	59.6	92	22	80.7
Labenz, 2005	Panto 40	A-D	1,596	1,156	440	72.4	141	183	88.5
	Eso 40		1,574	1,231	343	78.2	3	143	90.9
Schmitt, 2006	Ome 20	AD	572	379	193	66.3	491	81	85.8
	Eso 40		576	393	183	68.2	501	75	87.0

(36.3 ± 7.4 years, BMI 25.7 ± 4.6) and 1,829 men (36 ± 7.2 years, BMI 27 ± 3.7). Two out of four analyzed factors (varimax rotation) accounted for 51% of variability. Factor 1 (sialorrhea, dysphagia, odynophagia, retching) was associated to esophageal and upper respiratory symptoms (URS), and factor 2 (dyspnea, chronic cough, hoarseness, sleep disturbances) to pulmonary symptoms (PS). The body mass index (BMI) showed a direct association with PS (BMI: < 25: -0.068 ± 0.03 vs. 25-30: 0.012 ± 0.03 vs. > 30: 0.13 ± 0.04, p < 0.001). This suggests the hypothesis that age may be associated to URS, while factor 2 is associated to BMI (60).

The pathophysiological mechanisms of GERD-related chronic cough are (61): a) the intraesophageal acid that stimulates esophageal-tracheal-bronchial cough reflex; and b) micro-aspiration, if cough fits are correlated to acid GERD episodes it may be a sufficient cause, even with a normal 24-h pH; if the latter is abnormal, it does not necessarily mean it is the cause. The pathophysiological mechanisms of GERD-related asthma are: a) vagal reflex; b) bronchial hyper-reactivity; and c) micro-aspiration (62);

and those of chronic posterior laryngitis are: a) direct acid injury (laryngopharyngeal reflux); and b) vagal reflex that result in cough and throat clearing due to acid-related laryngeal injury (63). The frequency of abnormal exposure to acid in the latter is highly variable (17.5-79%) (64).

PHARMACOGENETIC EFFECTS OF CLINICAL PRACTICE WITH PPIs

Currently, when deciding on the appropriate PPI under this custom-tailored approach, it is of utmost importance to consider the adverse effects and drug interactions typically observed in patients taking PPIs.

Drug-drug interactions

The long-term use of PPIs can lead to drug interactions, especially in the elderly and patients with comorbidities.

Gastric acid suppression can increase (digoxin) or decrease (ketoconazole and itraconazole) the absorption of other drugs, or reduce their solubility, which is considered a drug class effect. PPIs have been reported to reduce the bioavailability of drugs up to 50%, and they can alter drug metabolism by induction or inhibition of the cytochrome P₄₅₀ enzymes, particularly in patients taking medications with a narrow therapeutic window (diazepam, phenytoin and warfarin) (27,65). The PPIs with greater potential for drug-drug interactions are omeprazole, esomeprazole and lansoprazole; pantoprazole has a lower potential for drug interactions (66). The decreased metabolism of CYP2C19 substrates is related primarily to omeprazole and esomeprazole. The following medications can be associated to clinically relevant effects: anticonvulsants, sedatives and muscle relaxants (phenytoin, mephenytoin, diazepam, flunitrazepam, phenobarbital, hexobarbital and carisoprodol); antidepressants (citalopram, escitalopram, fluoxetine, sertraline, venlafaxine, imipramine, clomipramine, trimipramine, amitriptyline, nortriptyline and moclobemide); propanolol, warfarin, progesterone, testosterone and cyclophosphamide (67). One of the most important drug interactions induced by omeprazole is a 25 ± 50% reduction in the clearance of diazepam, due to competitive inhibition of CYP2C19. Other interactions to be taken into account occur with alprazolam, chlorthalidone, clonazepam and midazolam. In patients on chronic benzodiazepine therapy, a PPI other than omeprazole or esomeprazole should be considered. PPI effects can be modified by interactions with other compounds (cimetidine, famotidine, fluoxetine, fluvoxamine, sertraline, isoniazide, ketoconazole, oral contraceptives, loratadine, tamoxifen and ticlopidine). Except for the common interactions of PPIs related to intragastric pH (ketoconazole, itraconazole and digoxin) only a few interactions are known for pantoprazole, rabeprazole and lansoprazole; furthermore, these PPIs do not cause interactions when coadministered with phenytoin, warfarin and diazepam (68).

Clopidogrel

The case of clopidogrel merits special mention. This anticoagulant reduces the risk of cardio-cerebrovascular disease –myocardial infarction (AMI), unstable angina, cerebrovascular accident and death–. It is transformed into its active metabolite by the cytochrome P₄₅₀. This conversion is inefficient in slow metabolizers. *In vitro*, CYP2C19 metabolism is competitively inhibited to a lesser extent by pantoprazole and rabeprazole than by omeprazole and esomeprazole. Genetic variations are associated with > 50% risk of adverse clinical events –cardiovascular (CV) death, AMI, and stent thrombosis– in patients receiving clopidogrel. Slow metabolizers and intermediate metabolizers with CYP2C19 GPM have been associated with decreased platelet inhibition and increased rate of CV events (69). In November 2009, the FDA issued an alert on the probable interaction between clopidogrel and omeprazole; their con-

comitant intake reduces clopidogrel's effectiveness. Subjects with decreased CYP2C19 function have lower platelet aggregation inhibition and are at higher CV risk. However, not all PPIs affect its metabolism. Even though the OR for CV events was 1.2-1.5 in observational studies, other studies do not show this effect (RR < 1.5-2.0). Current evidence does not support the conclusion that PPIs are related with CV events among clopidogrel's users. The FDA recommended avoiding the concomitant use of clopidogrel and drugs that inhibit CYP2C19. Although omeprazole and clopidogrel have both a short t_{1/2}, if their intake is kept apart by 12-20 h, theoretically, this competitive inhibition could be prevented (70). A meta-analysis of 23 clinical trials (CT) (93,278 patients) with substantial heterogeneity showed no direct association of CV events (19 CT, I₂ = 79%) and AMI (12 CT, I₂ = 77%) (RR 1.09, 95%CI: 0.94-1.26, p = 0.23, I₂ = 60%), but observational studies did show a significant association. Nevertheless, as above-mentioned, clopidogrel is a prodrug that requires activation by CYP2C19, and the competitive inhibition of the latter by omeprazole-esomeprazole explains their interaction. Pantoprazole is an alternative in subjects requiring clopidogrel, as the potential risk of ulcer-hemorrhage is present (71).

Adverse effects of PPIs

All PPIs are well tolerated, and there is no clear evidence of increased toxicity in slow metabolizers despite the increased AUC₀₋₂₄. Reported side effects include hip fracture, osteoporosis, hypovitaminosis specifically B₁₂, hypomagnesaemia, drug interactions, carcinoids, intrahospital infections, etc. The frequency of minor adverse effects is 1-3% (headache, diarrhea, nausea and rash), and serious adverse events (interstitial nephritis, hepatitis or visual disturbances) are very rare (72).

Hypergastrinemia, a physiological response to PPI acid suppression, shows large inter- and intra-individual variations. The use of PPIs may cause enterochromaffin-like cell hyperplasia, and fundic gland polyps (hyperplastic) that are rarely associated with dysplasia (73). A prospective study reported that PPI is an independent risk for hyperplastic polyps with odds ratio 9.0 (CI_{95%} 5.4-18.9, p < 0.0001) (74) but recently another retrospective study reported only 7.4% of them (75).

Bacterial overgrowth in the stomach may cause vitamin B₁₂ malabsorption, although not leading to deficiency, except in the elderly or in patients with Zollinger-Ellison syndrome on high PPI doses. PPIs do not affect vitamin D absorption. Inhibition of osteoclastic proton pumps reduces bone resorption, while acid suppression affects intestinal calcium absorption, and hypergastrinemia may enhance bone resorption (parathyroid gland hyperplasia) (5). Vitamin B₁₂ deficiency can increase fracture risk. The risk of hip fracture increases over time (1.62 > 5 years vs. 4.55 > 7 years) (76). An observational study (13,556 hip fracture cases and 135,386 controls) reported that PPI therapy for

over 1 year had a linear dose-response effect (OR 2.65; 95%CI, 1.80-3.90; $p < 0.001$). Adjusted OR was 1.44 (95%CI: 1.3-1.59; male OR 1.78; 95%CI, 1.42-2.22 > female OR 1.36; 95%CI, 1.22-1.53) ($p = 0.04$) and it is higher for osteoporosis and duration of use (1-year OR, 1.22 [95%CI: 1.15-1.30]; 2-year OR, 1.41 [95%CI: 1.28-1.56]; 3-year OR, 1.54 [95%CI: 1.37-1.73]; and 4-year OR, 1.59 [95%CI: 1.39-1.80]; $p < 0.001$ for all comparisons) (76). Current data do not support the risk of hip fracture with PPI use (77). Increased bacterial colonization of the stomach may be associated with pulmonary micro-aspiration and lung colonization in intubated patients who are chronic users of PPIs (76). While the use of PPIs does not increase the risk of hospital-acquired pneumonia, it does increase the risk of community-acquired pneumonia in a time-dependent fashion: 2-day OR, 6.53; 7-day OR, 3.79; 14-day OR, 3.21. However, chronic use does not increase this risk. Several case series have reported the development of interstitial nephritis as a class effect of PPIs in some susceptible individuals (79).

SOME PHARMACOECONOMIC ASPECTS

Several studies suggest that assessing the CYP2C19 genotype could be really helpful in determining the adequate dosage of PPIs. The cost-benefit of assessing the CYP2C19 genotype (mainly CYP2C19*1, CYP2C19*2 and CYP2C19*3) in a population of subjects on *Helicobacter pylori* eradication therapy where the frequency of slow metabolizers is 15%, could be approximately 5,000 dollars per patient (9). This is a cost-effective strategy that could enable us to apply adequately high doses in rapid metabolizers and low doses in slow metabolizers to achieve a more effective treatment and reduce costs and time.

CONCLUSIONS

All PPIs are generally effective in suppressing acid secretion; however, there are some differences that influence their antisecretory effects. Even though intragastric pH and acid secretion determine the acid load to the esophagus, the esophageal pH threshold ($\%t \text{ pH} < 4$) is the main factor of AAE in esophagus. When treating GERD symptoms with PPIs in clinical trials, the intragastric pH profile has shown great variability with wide 95% confidence intervals. Optimization of PPI use involves reduced variability, faster onset of action, sustained acid suppression, acid control, and an absorption independent of food intake. The longer the plasma $t_{1/2}$ is, the higher the AUC_{0-24} value, and hence the antisecretory effect. In non-erosive GERD, PPIs are less likely to improve abnormal esophageal pH.

The choice of a PPI should be guided by factors such as efficacy, safety, tolerability, quality of life, pharmacogenomics and cost-effectiveness. In other words, so as to “custom-tailor the best-fitting therapy” we need to answer the

questions for whom, for what, how and for how long, also taking into consideration symptom overlap (a subgroup of FGIDs show visceral hypersensitivity that has been related to a disturbance of the autonomic nervous system). Finally, PPI safety and tolerability are factors to be considered in elderly patients requiring chronic PPI use, who usually have chronic concomitant illnesses and therapies.

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