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Similarities and Differences between different proton-pump inhibitor formulations for the treatment of gastro esophageal reflux disease – A Review

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ABSTRACT

Gastro esophageal reflux disease is a chronic, recurrent disease that affects millions of people worldwide. Proton pump inhibitors are a group of drugs whose main action is a pronounced and long-lasting reduction of gastric acid production. These drugs are utilized in the treatment of many conditions such as Dyspepsia, Peptic ulcer disease, Gastro esophageal reflux disease. Currently proton pump inhibitors are available in both oral and injectable formulation. Proton pump inhibitors are substituted benzimidazoles that inhibit gastric acid secretion via inhibition of the gastric H+/K+ ATPase pump. Although there are some differences in pharmacokinetics and binding affinity for the pump, these drugs are comparatively similar in their efficacy in treatment of gastric diseases. The delayed release proton pump inhibitors effectively suppress gastric acid secretion and successfully treat acid-related disorders. Each differs somewhat in its formulations. The difference in the formulations has not been translated into clinical advantages over the delayed release proton pump inhibitors. Novel multiple formulations approaches are required for proton pump inhibitors to enhance acid suppression. Although the individual proton pump inhibitors have similar efficacy in many cases, differences between them should be considered when choosing a treatment regimen.

Keyword: Gastro esophageal reflux disease, Proton pump inhibitors, Pharmacokinetics

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INTRODUCTION

Gastroesophageal reflux disease (GERD) is a condition which develops when the reflux of stomach contents (into the esophagus) causes troublesome symptoms and / or complications[1]. Although different abnormalities in motility variables, such as lower esophageal sphinter function, esophageal paeristalsis and gastric motor activity can contribute to the development of GERD, the degree of esophageal acid exposure represents the key factor in its physiopathology[2]. It is a chronic often relapsing disease that if not treated approximately can lead to further complications including esophageal ulcers, stricture formation, obstruction, barrett's and esophageal cancer. In addition, GERD can potentially lead to extra-esophageal complications, such as worsening asthma-like symptoms and chest pain[3.] The main aim of the treatment of GERD is to relieve symptoms, promote normal growth and prevent the afore-mentioned complications. Conservative measures include parent reassurance, positioning and altering feed consistency. Treatment options include decreasing intra-gastric acidity with antacids, histamine H2 receptors blockers and Proton pump inhibitors (PPIs)[4]. This class of medications is among the most widely prescribed in the world, and our understanding of their clinical effects and of the differences among the various PPIs and their different formulations continues to grow. PPIs are a class of pharmaceutical compounds that inhibit gastric acid secretions by inhibiting H+/K+ - adenosine triphosphatase (H/K-ATPase) in parietal cells. This inhibition sufficiently raises and maintains gastric pH to exceed[4]. PPIs are now widely available in the world in US market such as omeprazole (available since 1989), lansoprazole (1995), pantoprazole (2000). Rabeprazole (1999), dexlansoprazole (2009), esomeprazole (2001), omeprazole magnesium (2003) and Ilaprazole are also available in some countries[5]. Different proton pump inhibitors and their availability are presented in Table-1.

Table 1: Different proton pump inhibitors with their brand name, FDA approval and their route of administration

PPIs Parameters	**OMP**	**LANS**	**PANT**	**RABP**	**ESOM**	**DEXLAN**	**OMP Mg**	**OMP + Sod. bicarbonate**	**OMP +Sod.bicarbonate**
Brand Name	PRILOSEC	PREVACID	PROTONIX	ACIPHEX	NEXIUM	DEXILANT	LOSEC	ZEGIRID	ZEGIRID OTC
Year of FDA Approval	Sep, 1989	May, 1995	Feb 2000	Aug, 1999	Feb, 2001	Jan, 2009	June, 2003	June, 2004	Dec, 2009
Route of Administr.	Oral, IV	Oral, IV	Oral, IV	Oral	Oral, IV	Oral	Oral	Oral	Oral

Note: OMP- Omeprazole; LANS- Lansoprazole; PANT- Pantoprazole; RABP- Rabeprazole; ESOM- Esomeprazole; DEXLAN- Dexlansoprazole; OMP Mg- Omeprazole magnesium; OMP+ Sod.bicarbonate- Omeprazole + sodium bicarbonate

PPIs rapidly degrade in acidic environments and therefore oral delivery of these compounds is challenging because the gastric pH is very acidic (typically between about pH 1 to 2. Under gastric conditions, PPIs typically degrade and are not readily available for uptake without being protected. Due to the pH sensitivity of PPIs, they typically are administered in a form that protects the drug from the gastric environment. Enteric coatings are probably the most widely used method of protecting acid-labile drugs (such as PPIs) from gastric degradation. Enteric coating methods typically form a barrier around drug particles, or an entire dosage form containing a PPI, with a coating that does not dissolve upon introduction to the low pH of the gastric environment. Such enteric coatings typically dissolve at a pH greater than 6, such as that found in the upper small intestine where the PPI is released in an environment where it will not significantly degrade, and therefore can be absorbed.

Historically, use of PPIs was limited to either the oral formulation or extemporaneous reformulation of these products for administration via nasogastric or enteral feeding tubes.[6-8] Recently, the number of commercially available PPI formulations has greatly expanded to include several oral formulations that may be administered enterally to patients unable to swallow a tablet or capsule (eg., immediate-release omeprazole with sodium bicarbonate packaged powder for suspension, a lansoprazole tablet that can be dissolved in water, esomeprazole pellets administered in water), as well as intravenous products (eg, esomeprazole, lansoprazole, pantoprazole).[9-16] With expansion of the PPI market as well as a broader array of formulations to choose from, clinicians are now faced with several issues when selecting PPI agents for inclusion in their formulary and/or hospital guidelines. While the introduction of new PPI products has expanded the therapeutic options for acid suppression in acutely ill patients, a number of unresolved questions remain surrounding the interchangeability of these products, the clinical significance of one PPI formulation over the other, and how oral/enteral PPI therapy should be used as step-down therapy after parenteral PPI therapy.

Pharmacological parameters and General Principles of PPIs

Gastric acid secretion occurs in response to endocrine, paracrine, and neurocrine via stimulation of the gastrin, histamine, and acetylcholine receptors located on the baso-lateral side of the parietal cell.[17,18] Although gastrin can directly stimulate acid secretion, gastrin also causes entero chromaffin-like cells to release histamine, which in turn activates the histamine receptor located on the basolateral surface of the parietal cell. Activation of basolateral receptors leads to the release of

secondary messengers triggering protein kinases within the parietal cell, culminating in activation of the hydrogen potassium adenosine triphosphatase (H/K-ATPase) enzyme (ie, proton pump), the final step in acid secretion.[17-19] To maintain intracellular electroneutrality, the proton pump exchanges intracellular hydrogen ions for luminal potassium ions on a one-to-one basis, thus "pumping" hydrogen ions into the lumen. Proton-pump inhibitors gastric acid secretion inhibition mechanism was represented in Figure-1.

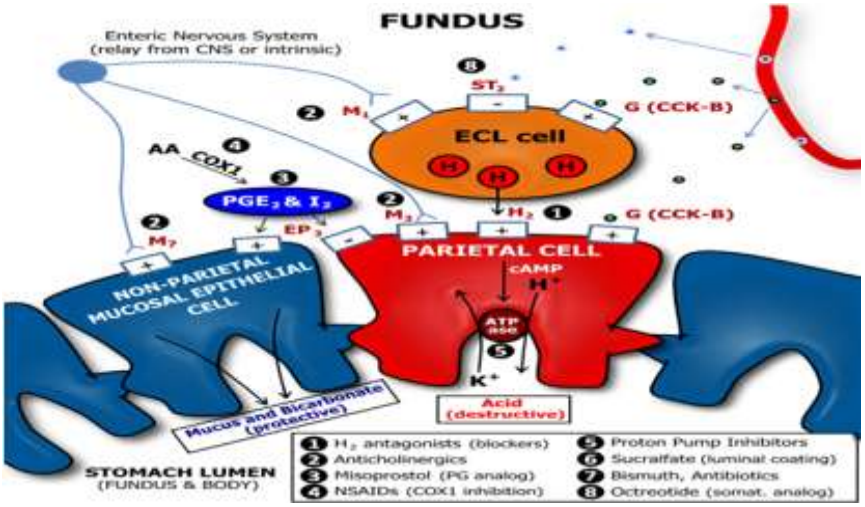

Figure 1: Proton-pump inhibitors gastric acid secretion inhibition.

PPIs are substituted 2-pyridyl methyl-sulfinyl benzimadazole that covalently bind to the hydrogen-potassium adenosine triphosphatase (H/K-ATPase) enzyme, thereby inhibiting in a dose- dependent manner the final step in gastric acid secretion[17, 20, 21]. Since PPIs block the final step in acid secretion, they are more potent inhibitors of acid secretion than the histamine (H)**2**- receptor antagonists, which block only one pathway involved in acid secretion[21]. In addition, unlike H**2**-receptor antagonists, tolerance does not develop to PPIs[22]. Consequently, due to their ability to profoundly inhibit acid secretion and lack of tolerance, PPIs have become the preferred agents for many conditions, particularly in situations of persistent or severe disease.[17] The oral PPI formulations are designed as enteric-coated delayed-release products or are coadministered with bi- carbonate to protect the drug from premature activation in the acidic environment of the stomach[11,19]. Once these formulations reach the duodenum, the un-protonated prodrug is absorbed. The un-protonated compound readily penetrates across cell membranes; once it transverses the parietal cell and is exposed to the acid environment, it becomes protonated and trapped within the secretory canaliculus[17]. Protonation initiates a series of chemical rearrangements that leads to formation of the active moiety, which binds to the cysteine residues within the proton pump, inhibiting acid secretion. Binding to cysteine residue 813 or 822 within the fifth and sixth transmembrane domains of

H/K-ATPase is key for inhibition of acid secretion. All of the currently marketed PPIs bind to cysteine residue (either cysteibne-813or cysteibne-822) [23, 24].

The PPIs differ in terms of their pKa values, with rabeprazole having the highest (5.0) and pantoprazole the lowest (3.96) values. The pKa value, in concert with the pH of the environment, influences the degree of accumulation of the agent within the parietal cell, rate of activation, and acid stability; however, the clinical relevance of these differences is questionable [19, 20, 23].

PPIs inhibit only active proton pumps. It is estimated that, following a meal, 70 – 80% of proton pumps will be activated and consequently available for inhibition by a given dose of a PPI. Subsequent doses will inactivate more active pumps, including those that were not inactivated the previous day, as well as newly synthesized pumps. Overall, with once-daily dosing, it takes approximately 3–4 days to achieve maximum inhibition of acid secretion and pharmacodynamic steady-state.

Pharmacokinetics

The pharmacokinetic characteristics of the PPIs marketed in the US are represented in Table 2.[25-29] As expected, due to high first-pass metabolism, the plasma AUC profiles and bioavailabilities of the oral PPI formulations are lower than those seen following intravenous administration. The oral bioavailability of omeprazole and esomeprazole increases over the first 5 days of therapy[30-32]. Increase in AUC and bioavailability seen with omeprazole and esomeprazole during that time results from a decrease in first-pass extraction. This is likely the result of decreased acid degradation within the gastric lumen, as gastric pH increases over the first few days of therapy, as well as inhibition of those drugs own metabolism. Unlike omeprazole and esomeprazole, the oral bioavailabilities of lansoprazole, pantoprazole, and rabeprazole are consistent over time.

Table 2: **Pharmacokinetic Parameters of Oral Proton Pump Inhibitors**

Parameter	Dexlanso prazole	Esome prazole	Lanso prazole	Ome prazole	Panto prazole	Rabe prazole
Bioavailability (%)	—	64-90	80-85	30-40	77	52
Time to peak plasma concentration (h)	1-2; 4-5	1.5	1.7	0.5-3.5	2-3	2-5
Protein binding (%)	96	97	97	95	98	96.3
Half-life (h)	1-2	1-1.5	1.6	0.5-1	1-1.9	1-2
Primary route of excretion	Hepatic CYP2C19 CYP3A4	Hepatic CYP2C19	Hepatic CYP2C19	Hepatic CYP2C19	Hepatic CYP2C19 CYP3A4	Hepatic CYP2C19
Excreted unchanged in urine	0%	< 1%	0%	0%	0%	0%

Food impairs the extent of absorption of lansoprazole and esomeprazole and delays absorption of

pantoprazole and rabeprazole, further emphasizing the need to administer PPIs prior to a meal (i.e., when pumps become activated). Whether food affects the bioavailability of omeprazole is controversial; however, the manufacturer recommends that continuous enteral feedings be suspended for 1 hour prior to and 3 hours following administration of immediate-release omeprazole in bicarbonate suspension when it is administered via a nasogastric tube [33-34].

The relative bioavailabilities of extemporaneously prepared PPI sodium bicarbonate formulations are notably lower than the intact oral capsule or tablet (lansoprazole 68 – 85%, omeprazole 49 – 81%, pantoprazole 75%). This is likely the result of acid degradation and/or inadequate delivery. Similarly, the absolute bioavailability of the commercially available omeprazole bicarbonate rapid-release product is only 30-40%. In contrast, the relative bioavailability of lansoprazole rapid-disintegrating tablets administered either as the intact tablet or as pellets in water via an 8 French nasogastric tube to healthy volunteers has been shown to be similar to that achieved with the oral capsule. The bioavailability of esomeprazole pellets administered in water via a 16 French nasogastric tube to healthy volunteers is also similar to that of the oral intact capsule[10].

Proton pump inhibitors undergo stereo selective metabolism. For example, when omeprazole is administered, the *R*-enantiomer is rapidly cleared by the liver, but the *S*-enantiomer is cleared much more slowly. Stereo selective metabolism explains the differences in the pharmacokinetics of esomeprazole compared with omeprazole. Since esomeprazole is a single enantiomeric product (*S*-isomer of omeprazole), it has a slower clearance than omeprazole. The AUC for esomeprazole has been shown to be 20-60% higher than that of omeprazole, depending on CYP2C19 phenotype[30].

FORMULATION OF PROTON PUMP INHIBITORS FOR ORAL ADMINISTRATION

The PPIs employing in any form of delayed-release formulation, the manufacturers of these drugs recommend that they should not be chewed or crushed. Omeprazole and lansoprazole are available as enteric-coated granules in capsules; whereas esomeprazole contains enteric-coated pellets in capsules, oral granules and tablet dosage form. Pantoprazole and rabeprazole are only available as delayed release enteric-coated tablets. Alternative oral dosage formulations have been developed for ease of administration in particular patient subgroups. For example a new oral suspension formulation of lansoprazole (Prevacid) was FDA-approved in 2001 and in 2002 lansoprazole as orally disintegrating tablets (LODT), in 2004 FDA approved Omeprazole immediate-release powder for oral suspension in both 20mg and 40mg dose strengths.

Other methods of administering omeprazole, lansoprazole, or esomeprazole have been recommended for patients who are unable to swallow intact capsules. The capsules may be

opened and the granules sprinkled over a tablespoon of applesauce, pudding, yogurt, or cottage cheese; the food must be swallowed immediately without stirring, crushing, or chewing. In patients with nasogastric or gastrostomy tubes, the granules in one capsule may be mixed with 40 mL of apple juice and injected through the tube, which should be flushed with additional juice to clear the tube. The marketed formulations of the PPIs limit their use to patients that can swallow. However, some of the PPIs can be made into a liquid formulation, permitting their use for patients that cannot swallow, have difficulty swallowing, or have gastric feeding tubes. The following are preparations the pharmaceutical manufacturers suggested and have been evaluated for bioavailability relative to the capsule or tablet form. Formulations of various PPI's are represented in Table 3.

Table 3: Proton pump Inhibitor formulations

PPI	**Panto prazole**	**Rabe prazole**	**Ome prazole**	**Esome prazole**	**Omeprazole / Sodium bicarbonate**	**Dexlansoprazole**	**Lanso prazole**
Main Oral dosage forms	DR Tablets	DR Tablets	DR Capsules	DR Capsules	IR Capsules	DDR Capsules	DR Capsules
Contents	-	-	EC pellets	EC pellets	Powder	Dual delayed release pellets	EC pellets
Strengths available	20, 40mg	20mg	10, 20 & 40mg	20 & 40mg	20 & 40mg	30 & 60mg	15 & 30mg
Other Dosage forms	IV injection	-	DR suspension	DR suspension & Powder for IV injection	-	-	DR Orally Disintegrating tablets, Simplified Lansoprazole suspension & DR suspension

DR-delayed release, **EC**-Enteric coated, **IR**-Immediate release, **DDR**-Dual delayed release, **IV**-Intra venous

Six PPIs are currently available in the US market. All PPIs are available in an oral dosage form however, only lansoprazole, omeprazole and pantoprazole are available generically. Omeprazole was the first over-the-counter PPI, which became available in 2003. An OTC formulation of Prevacid has received FDA approval, and has been available since November 2009. Nexium was recently approved for use in the treatment of symptomatic GERD and erosive esophagitis in pediatric patient. Protonix also recently received a new indication and is now approved for the short term treatment of erosive esophagitis associated with GERD in pediatric patients.

Dexlansoprazole the most recently approved proton pump inhibitor, is now being marketed under the name dexilant. Dexilant is an R-isomer of lansoprazole with a dual delayed release concentration–time profile that has two distinct peaks: the first occurs 1-2 h after administration and the second within 4-5h. The FDA approved marketed formulations of PPIs are represented in Table 4.

Table 4:FDA approved proton pump inhibitors formulation, brand name and generic product availability

Generic Name	Brand Name	Manufacturer	Generic product availability
Dexlansoprazole	Dexilant(formerly Kapidex)	Takeda	Not available
Esomeprazole	Nexium	AstraZeneca	Available
Lansoprazole	Prevacid	Takeda	Available
	Prevacid Solutab		Not available
	Prevacid 24hr		Not available
Omeprazole	Prilosec, Prilosec OTC	AstraZeneca	Available
Omeprazole + Sodium bicarbonate	Zegerid OTC	Santarus	Available
Pantoprazole	Protonix	Wyeth Pharms, Inc	Available
Rabeprazole	Aciphex	Eisai	Available

Alternative Oral delivery and dosage methods

Many hospitalized patients who require PPI therapy cannot swallow a tablet or capsule, and a formulation that can be administered as a suspension through a feeding tube or parenterally is required. These would include most patients admitted to the intensive care unit, those having undergone recent gastrointestinal tract surgical procedures, patients with dysphagia (eg, recent stroke), and children. Similar to other products, such as fluoroquinolones or H_2-receptor antagonists, one should select the appropriate formulation and route of administration based on the individual patient characteristics. With PPIs not being available in US in an intravenous dosage form until 2001, clinicians relied primarily over the past decade on intact granule administration or preparation of a PPI suspension with water, juice, or sodium bicarbonate when the administration of a capsule or tablet was contraindicated. More recently, commercial suspensions and an oral dissolving tablet have become available[35,36]. These various delivery methods are outlined in Table-4. Intravenous PPI therapy has been used as an alternative to a PPI suspension in this population, particularly when questions surrounding the absorption of the suspension exist or in patients with recent non variceal upper gastrointestinal bleeding.[37]

It should be noted that the majority of available data evaluating alternative dosage methods have been conducted in healthy volunteers and patients with GERD and few have been conducted in

hospitalized, intensive care unit, and pediatric patients the groups most likely to need and benefit from the use of alternative dosing methods.[38-40] The alternative dosing methods of PPIs are represented in Table-5.

Table 5: Alternate oral delivery methods for PPIs

Dosage form	Esomeprazole	Lansoprazole	Omeprazole	Pantoprazole	Rabeprazole
Rapid disintegrating tablet	No	Yes**a**	No	No	No
Commercially available suspension	No	Yes**a,b**	Yes**a,c**	No	No
Bicarbonate-based suspension	No**d**	Yes	Yes	Yes	No
Direct enteral administration via NG or OG tube	Yes**e**	No	No**f**	No	No
Apple or orange juice	Yes**a**	Yes**a,g,h**	Yes	No	No
Applesauce	Yes**a,i**	Yes**a,j**	No	No	No

NG = nasogastric; OG = orogastric; PPIs = proton pump inhibitors.

aFood and Drug Administration–approved indication.

bLansoprazole suspension administration through small enteral feeding tubes is not recommended by the manufacturer.

cAvailable as a powder for oral suspension containing omeprazole and 1680 mg of sodium bicarbonate.

dDissolution occurs very slowly, if at all, when exposed to sodium bicarbonate.

eWhen flushed with 50 mL of water, >98% is delivered; when flushed with 25 mL of water, only 77% is delivered.

fPellets become sticky when mixed with water; thus, this is not recommended for NG or OG tube administration.

gFor NG administration, drug must be mixed in 40 mL of apple juice and the tube flushed with apple juice after administration.

hFor oral administration, capsule contents must be mixed in 60 mL of apple, orange, or tomato juice.

iStable in milk, water, orange juice, yogurt, or cultured milk, but bioavailability has not been determined.

jAlso can be administered in Ensure, pudding, cottage cheese, yogurt, or strained pears.

Intact Granule Administration

To maximize acid suppression of any PPI, delivery to the activated parietal cell as the un-protonated pro-drug form is essential. This poses a dilemma in that all commercially available PPIs in solid dosage forms exist as enteric-coated delayed-release tablets or microencapsulated beads packaged in a capsule; all are designed to prevent exposure to gastric acid. Results of early attempts to administer contents of a PPI capsule through a nasogastric tube followed by water flush were mixed. When omeprazole and lansoprazole are removed from the capsule and mixed with water (pH >5), the destruction of the enteric coating will lead to premature activation and erratic absorption. In addition the destruction of the enteric coating will lead to the formation of insoluble beads that may stick to tubing, particularly with narrower tubes (eg, 8 French).[36-42]

Table 6: Comparison of commercially available Intravenous PPIs

Parameter	Esomeprazole	Lansoprazole	Pantoprazole
FDA-approved indications	GERD[a]	GERD[a]	GERD,[a] Zöllinger–Ellison syndrome[b]
intravenous bolus	3 min	not approved	2 min in 10 mL
intravenous infusion	10–30 min in 50 mL	30 min in 50 mL	15 min in 100 mL
In-line filter	no	yes	no
Dedicated intravenous line	yes[c]	no[d]	yes[d]
Compatibility	D5W, saline, LR	D5W, saline, LR	D5W, saline, LR
pH of reconstituted solution	9–11	11	9–10.5
Storage temperature (°C)	25; protect from light	25; protect from light	20–25; protect from light
Reconstituted stability	12 h at room temperature 12 h in saline and LR 6 h in D5W at room temperature	1 Hr 24 h in saline and LR 12 h in D5W at room temperature	2 Hr 22 h after dilution at room temperature
Y-site compatibility	NA	ongoing study	selected drugs
Infusion-related reactions	1.7% (mild focal erythema and pruritus)	1% injection pain	<1% thrombophlebitis

D5W = dextrose 5% in water;; GERD = gastroesophageal reflux disease; LR = lactated Ringer's; NA = not available; PPIs = proton pump inhibitors; saline = NaCl 0.9%.

[a]Short-course treatment of GERD in patients unable to swallow oral medications.

[b]At doses up to 80 mg every 8 hours.

[c]Stable for 18 hours if left in the vial and an additional 6 hours with an admixture.

[d]Compatibility with other agents is unknown. Line should be flushed before and after administration. No other intravenous medications should be ad- ministered concurrently

Immediate Release PPIs

An alternative to direct granule administration is the placement of the PPI in sodium bicarbonate. Sodium bicarbonate not only dissolves the enteric coating, but prevents the formation of insoluble material and purportedly neutralizes gastric acid to prevent proportion of the PPI prior to absorption. This approach was first documented in 1985 with omeprazole and later with both lansoprazole and pantoprazole.[43, 44]

An immediate-release unit dose packet of flavored powder for oral suspension containing 20 mg of omeprazole and 1680 mg or 20 mEq of sodium bicarbonate was approved by the FDA in June 2004. The product is designed for bed time administration with the contents of the packet emptied into a small cup containing 2 tablespoons of water, then administered orally.

Orally disintegrating tablets

Lansoprazole is the only PPI available in a delayed-release, orally disintegrating tablet.[26] The 15-

or 30 –mg strawberry-flavored tablet is mixed in 5 mL water and ad ministered either orally or through a nasogastric tube of ≥8 French diameter or allowed to disintegrate after placement on the tongue. Like the suspension packets, the disintegrating tablet is designed for bed time administration.

Intravenous PPI formulations

Currently, 3 intravenous PPIs (esomeprazole, lansoprazole, pantoprazole) are available in the US market.[13, 14, 16] the similarities and differences among the three intravenous PPIs were presented in Table 6. A major difference between these agents is rate of administration. Both esomeprazole and pantoprazole may be given as a rapid intravenous infusion (over 3 and 2 min, respectively) and a slow infusion (10–30 and 15 min, respectively). Lansoprazole is approved only for a 30 minute infusion and must be administered through a 1.2 µm pore size in-line filter. The original pantoprazole label required filtration; however, recent formulation changes allow for administration without the in-line filter.

Esomeprazole does not require a filter for administration. All PPIs should be administered through a dedicated intravenous line and flushed with a compatible solution both before and after administration. Although the product label for lansoprazole does not require a dedicated line.

Drug interactions

PPIs cause significant increases in gastric pH, which may alter the absorption of weak acids or bases. They may inhibit the absorption of drugs such as griseofulvin, ketoconazole, Itraconazole, iron salts, vitamin $B_{12,}$ cefpodoxime and enoxacin many of which are weak bases and require acid for absorption.[20, 45-47] Co-administration with these agents should be approached cautiously because it may result in clinical treatment failure. The effects of PPIs on several medications i.e., drug interactions of PPIs were represented in Table- 7.

Table 7: PPIs drug interactions

Drug	Omeprazole	Lansoprazole	Pantoprazole	Rabeprazole	Esomeprazole	Dexlansoprazole
Carbamazepine	↓Metabolism	Unknown	None	Unknown	None	Unknown
Clarithromycin	*	None	Unknown	Unknown	None	Unknown
Diazepam	↓Metabolism	Unknown	None	None	None	None
Digoxin	↑Absorption	Unknown	↑Absorption	↑Absorption	↑Absorption	↓Absorption
Ketoconazole	↓ Absorption	↓ Absorption	Unknown	↓Absorption	↓Absorption	↓Absorption
Methotrexate	↓ Renal excretion	Unknown	Unknown	Unknown	Unknown	Unknown
Nifedipine	↑Absorption	Unknown	↑Absorption	Unknown	Unknown	Unknown
Phenytoin	↓Metabolism	None	None	None	Unknown	Unknown
Warfarin	↓Metabolism	None	None	None	Increases INR	Increases INR
Theophylline	None	↑Metabolism	None	None	Unknown	None

PPIs = proton pump inhibitors; ↓ = decreased; ↑ = increases

*Omeprazole increases gastric mucus concentration of clarithromycin, and clarithromycin inhibits cytochrome P450 metabolism of omeprazole.

Rabeprazole (Aciphex)	20-mg tablet, Delayed release, enteric coated, oral	Do not cut, crush, or chew.

ODT- orally disintegrating tablet; **OTC**- over-the- counter; **tbsp**- tablespoon.

Dosage and administration

PPIs are inactivated by exposure to gastric juice and are delivered in delayed-release gelatin capsules containing enteric-coated granules (omeprazole and lansoprazole) or in delayed-release enteric-coated tablets (rabeprazole and pantoprazole)[20, 26-28, 48]. Omeprazole is supplied in doses of 10, 20, and 40 mg, and lansoprazole is supplied in doses of 15 and 30 mg. Both of these agents should be taken 30 minutes before meals and their capsules should not be opened, chewed, or crushed, but should be swallowed as whole. Other methods of administering omeprazole, lansoprazole, or esomeprazole have been recommended for patients who are unable to swallow intact capsules. The capsules may be opened and the granules sprinkled over a tablespoon of applesauce, pudding, yogurt, or cottage cheese; the food must be swallowed immediately without stirring, crushing, or chewing. In patients with nasogastric or gastrostomy tubes, the granules in one capsule may be mixed with 40 mL of apple juice and injected through the tube, which should be flushed with additional juice to clear the tube. Dosage for instructions for patients were represented in Table 8.

Table 8: Dosage form instructions for patient

Drug	Formulations	Instruction
Dexlansoprazole (Dexilant)	30mg and 60mg capsules, Delayed release, Oral	Do not crush or chew. Capsules should be swallowed whole; as a alternative in patients unable to swallow, open capsule and sprinkle intact granules in 1tbsp of applesauce
Esomeprazole (Nexium)	20mg and 40mg capsules, Delayed release, Oral 10mg, 20mg, 40mg granules packet for suspension, Delayed release, Oral 20mg and 40mg powder for reconstitution for intravenous (IV) injection	Do not crush or chew oral capsules. Capsules can be opened and contents mixed with 1 tbsp applesauce; mixture should not be chewed. Nasogastric tube: Capsules (opened) and granules are used according to specific manufacturer labeling directions.

Lansoprazole (Prevacid)	15-and 30-mg capsules, Delayed release, oral 15-mg Delayed release capsule, oral, 24 hour 15- and 30-mg Delayed release tablets, ODTs; contain phenylalanine; strawberry flavor	Capsules may be opened and sprinkled on cottage cheese, yogurt, strained pears, or Ensure pudding, or emptied into 60 mL of orange/apple/tomato juice. ODTs should not be swallowed whole, broken, cut, or chewed. Nasogastric tube: Capsules and ODTs may be used according to specific manufacturer labeling directions.
Omeprazole (Prilosec)	20-mg capsules, oral 10-, 20-, and 40-mg capsules, Delayed release, oral 2.5-and 10-mg granules packet for suspension, Delayed release, enteric coated, oral 20-, 40-mg Delayed release tablet, oral OTC: 20-mg tablet, enteric coated	Capsules should be swallowed whole; delayed-release capsule may be opened and contents added to 1 tbsp of applesauce. Tablets should be swallowed whole—do not crush or chew. Nasogastric tube: Capsules and oral suspensions may be used according to specific manufacturer labeling directions.
Omeprazole/ Sodium Bicarbonate (Zegerid)	20 mg/1100 mg and 40 mg/1100 mg capsules 20 mg/1680 mg and 40 mg/1680 mg powder packets for oral suspension OTC: 20 mg/1100 mg capsule, oral	Capsules should be swallowed whole and should not be opened, sprinkled on food, or administered via Nasogastric tube. Capsules should not be crushed or chewed. Powder for oral suspension should be mixed with 2 tbsp water. Nasogastric tube: Oral suspensions may be used according to specific manufacturer labeling directions.
Pantoprazole (Protonix)	20- and 40-mg tablets, Delayed release, oral 40-mg granule packet for suspension, Delayed release, enteric coated, oral 40 mg powder for reconstitution for intravenous (IV) injection	Tablets should be swallowed whole—do not crush or chew. Oral suspensions are administered only in apple juice or applesauce. Do not administer with any other liquid (eg, water) or food. Nasogastric tube: Oral suspensions may be used according to specific manufacturer labeling directions.

Rabeprazole is supplied in one dose of 20 mg, and pantoprazole (Protonix) is supplied in one dose of 40 mg. Both agents must be swallowed whole without crushing, chewing, or splitting. Rabeprazole should be taken after meals, but pantoprazole may be taken without regard to meals. Antacids may be administered concomitantly with all PPIs. Dosage adjustments for PPIs are not necessary in elderly patients or those with renal failure or mild hepatic impairment. Lansoprazole, rabeprazole, and pantoprazole should be used with caution in patients with severe hepatic impairment The FDA has not approved pantoprazole for maintenance therapy because safety has not been established beyond 16 weeks. At this time, pantoprazole is indicated by the FDA only for the treatment of erosive esophagitis in a dosage of 40 mg daily for eight to 16 weeks. It is the only PPI available for intravenous administration and has recently been approved by the

FDA for the short-term intravenous treatment (seven to 10 days) of GERD in hospital in-patients who are unable to take an oral PPI. The intravenous dosage is the same as the oral dosage (40 mg) and should be administered slowly over 2 to 15 minutes.

Esomeprazole is the s-isomer of omeprazole. It is more bioavailable than omeprazole as the result of a lesser first-pass effect and slower plasma clearance. Esomeprazole in dosages of 20 and 40 mg produce higher 24-hour intragastric pH levels than omeprazole, thus possibly resulting in superior acid control. The incidence and types of adverse effects appear to be similar to those of omeprazole. [50]

Esomeprazole is supplied as delayed-release capsules containing enteric-coated pellets and is available in doses of 20 and 40 mg. It should be taken one hour before meals, and dosage adjustment is not necessary in elderly patients or those with mild to moderate hepatic impairment. Daily dosages should not exceed 20 mg in patients with severe hepatic impairment.

CONCLUSION

PPIs are much superior to H2 receptor antagonist in the treatment of acid related diseases. Therefore, PPIs may be more cost-effective than H_2 blockers, especially in patients with more severe acid-peptic disorders, because of their lower and less frequent dosing requirements and their comparatively shorter duration of required therapy. The DR-PPIs effectively suppress gastric acid secretion and successfully treat acid-related disorders. There are only minor differences among existing members of the class, and these have not been translated into consistent, clinically meaningful advantages for any individual DR-PPI. The drugs enteric coated impair their systemic absorption, and may delay the onset of maximal antisecretory effect. Alternative dosing formulations may be more convenient for some specific groups of patients but still rely on some form of enteric coating. The PPIs may be considered for therapeutic interchange because of their comparable pharmacologic properties and clinical efficacy and safety profiles. In general, PPIs are therapeutically comparable at the same dosage levels (Half-standard- or double dose). Most studies have not shown a significant difference between the six proton pump inhibitors used in standard doses for the healing of reflux oesophagitis or duodenal ulcer. However trends for earlier symptom relief from oesophagitis and more rapid healing of duodenal ulcers were seen with lansoprazole. The few reported studies of PPIs use in gastric ulcer healing suggest that there may be advantage in using the PPI that have a higher standard dose. H. Pylori eradication rates are similar when the different PPIs are used in triple therapy regimens. Finally, important evidence indicating that PPI therapy may be useful for some extraesophageal manifestations of GERD and that twice-daily therapy

may be the optimal approach for such symptoms continues to accumulate, providing important data for primary care physicians and gastroenterologists alike.

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