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Frovatriptan (Frova®): A new Triptan

Trinh Kieu, Pharm.D. Candidate

Introduction

Migraine headaches are characterized by attacks of intense throbbing head pain which is typically unilateral. In addition, nausea, vomiting, or sensitivity to light, sound or movement often accompany the headache. When untreated, these attacks typically last 4 to 72 hours. Migraine's prevalence worldwide is estimated at 12%, with a higher prevalence in women (15%-18%) compared to men (6%). It is estimated that in the United States there are about 28 million people who suffer from migraine headaches.[1] Unfortunately, a significant number of these people have not been adequately treated.[2]

In the last decade, elucidation of the neurochemical etiology of vascular headaches, particularly migraine attacks, has led to the development of the "triptan" family of antimigraine agents.[3] Frovatriptan (Frova®) is the newest addition to the triptan class. It is manufactured by Elan Pharmaceuticals Inc., and was approved by the FDA in November 2001 for the acute treatment of migraine attacks with or without aura in adults. Pertinent pharmacology, pharmacokinetics, clinical trials, adverse drug reactions, drug interactions, dosage, and cost of frovatriptan will be reviewed in this article.

Pharmacology/ Pharmacokinetic

Similar to other members of the triptan family, frovatriptan is a serotonin (5-HT) receptor agonist that binds with high affinity to the 5-HT_{1B} and 5-HT_{1D} receptors. Pharmacological actions that have been implicated in the antimigraine effect of the triptans include: stimulation of presynaptic 5-HT_{1D} receptor (which serves to inhibit both dural vasodilatation and inflammation), and direct inhibition of trigeminal nuclei cell excitability via 5-$HT_{1B/1D}$ receptor agonism in the brainstem. More importantly, frovatriptan causes vasoconstriction of meningeal, dural, and cerebral vessels after binding to the 5-HT_{1B} receptor.[1] Unlike the other triptans, frovatriptan is a partial agonist to the 5-HT_{1B} receptor, and it is the most potent triptan in producing contraction of human basilar arteries.[4]

Frovatriptan demonstrates a distinct functional selectivity for cerebral circulation causing an increase in cerebrovascular resistance with little or no peripheral effects.[1] The oral bioavailability of frovatriptan varies from 22% to 30%. Although the time to maximum concentration is 2-3 hours after oral administration, approximately 60-70% of the plasma maximum concentration is achieved within 1 hour of dosing. Frovatriptan is 15% bound to plasma proteins. It distributes into erythrocytes with binding that is reversible and time dependent. Importantly, frovatriptan has a half-life of approximately 26 hours, which is substantially longer than any of the other triptans developed to date. Metabolism of frovatriptan is mediated primarily by the hepatic isoenzyme CYP1A2, and is cleared by both the kidneys and the liver. Although renal elimination contributes significantly to frovatriptan clearance (50%), renal impairment does not have a significant effect on the pharmacokinetics of frovatriptan since the liver has sufficient capacity to compensate. Frovatriptan can be taken without regard for food, and there is no need for dosage ad-

Table 1. Review of Frovatriptan Clinical Studies

Reference	Study Design	N	Results
Rapoport et al [6]	R, PC, DB, PG,	1453	Frovatriptan was well tolerated throughout the dose range of 0.5 to 40 mg. The 2.5-mg dose gives the optimal balance of efficacy and tolerability for the acute treatment of migraine.
Goldstein et al [7]	R, DB, PC, PG, MC	635	The 2.5-mg dose of frovatriptan offers optimal tolerability and efficacy the treatment of acute migraine. Higher doses do not appear to confer greater efficacy and are associated with an increased incidence of adverse effects.
Ryan et al [8]	R, PC, DB, PG, MC.	2676	Frovatriptan represents a consistently effective acute treatment for migraine and accompanying symptoms.
Geraud et al [9]	R, OL, PC, DB, PG, MC	2392	Frovatriptan 2.5 mg was well tolerated by a wide variety of patients. Adverse events profile was found similar to that of placebo.

R=randomized; DB=double-blind; MC=multicenter; PC=placebo-controlled; PG=parallel group; OL=open label.

justment in the elderly, or in women taking a combined oral contraceptive.[4]

Clinical Trials

Limited number of clinical trials are available which evaluate the efficacy, tolerability and safety of frovatriptan. Table 1 summarizes some of the clinical trials reviewed in this paper.

Rapoport et al.[6] evaluated the optimum dose of frovatriptan for the acute treatment of migraine. The study was a double-blind, randomized, placebo-controlled, 2 dose parallel-group trial. Patients (n=1453) were randomly assigned to frovatriptan or placebo. The dose studied ranged from 2.5 to 40 mg in the high-dose study and 0.5 to 5 mg in the low-dose study. In the high-dose study, patients were randomized to take placebo or frovatriptan 2.5 mg, 5 mg, 10 mg, 20 mg, or 40 mg. Patients in the low-dose study were to take placebo or frovatriptan 0.5 mg, 1 mg, 2.5 mg. The medication was taken at the onset of a moderate or severe migraine. Patients were evaluated in the clinic on two occasions, at screening and at a follow-up visit within 5 working days following the treatment. Efficacy and tolerability were measured based on a 4-point scale according to International Headache Society criteria.[6] Frovatriptan 2.5 mg was observed as the lowest effective dose with an approximate two-fold magnitude of effect compared to placebo (40% versus 23%; P<.001).

A separate study was conducted to investigate the efficacy and tolerability of 0.5, 1, 2.5, or 5 mg doses of frovatriptan compared to placebo in patients with acute onset of moderate or severe headache attacks. This randomized, double-blind, parallel-group, placebo-controlled trial was conducted in various centers throughout the United States. Patients suffering from migraines with or without an aura were randomized to receive placebo, 0.5, 1, 2.5, or 5 mg of frovatriptan. Patients received the study medication at the onset of a moderate or severe migraine headache and recorded headache intensity, functional impairment, and migraine-associated symptoms over 24 hours. The primary efficacy parameter was headache relief at 2 hours, defined as the proportion of patients in whom headache severity changed from moderate/ severe to mild or no headache. Secondary efficacy measures included: headache response at 4 and 6 hours. Out of 695 randomized patients, 635 patients completed the study. Headache response 2 hours postdose in patients who took frovatriptan 2.5 mg (38%) was significantly higher than in the placebo group (25%; P<0.05). Headache response with frovatriptan 5 mg (37%) was also superior to placebo at 2 hours postdose. The response with frovatriptan 0.5 and 1 mg were comparable to placebo (26% and 20%, respectively). The author concluded that frovatriptan 2.5 mg is the lowest effective dose for the treatment of acute migraine. Also, higher doses did not appear to offer greater efficacy and were associated with an increase in the incidence of adverse effects.[7]

To confirm the clinical efficacy of frovatrip-

tan 2.5 mg, three randomized, placebo-controlled, double-blind, parallel-group trials were performed by Ryan et al.[8] The studies were carried out throughout Europe and North America. Of the total of 2194 patients, 740 (27.6%) were randomized to receive placebo and 1454 (72.3%) were randomized to receive frovatriptan 2.5mg. Up to three attacks were treated with the study medication and a consistent response was achieved among patients on frovatriptan 2.5 mg compared with placebo. The difference between frovatriptan and placebo was approximately two-fold (P<0.001). Frovatriptan 2.5 mg provided significant pain relief over placebo at 2, and 4 hours postdose. Frovatriptan was also significantly superior to placebo at rendering patients pain-free, (9%-14%) compared with 2% to 3% for placebo (P<0.001). One-third of the patients experienced relief from the headache within 1.3 to 1.7 hours, and in the majority of the patients this relief did not cease. Migraine related symptoms were relieved faster with frovatriptan compared with placebo. Fifty-seven percent to 64% of patients with frovatriptan had no or mild functional impairment compared with 35% to 43% of patients in the placebo group. The results of the studies indicate that frovatriptan 2.5 mg provides reliable and effective acute treatment for migraines and accompanying symptoms.[8]

Geraud et al.[9] reviewed four short-term studies that evaluated the tolerability and safety of frovatriptan 2.5mg in a total of 2392 patients. These double-blinded, randomized, placebo-controlled, open-label trials, randomized 1554 patients to frovatriptan and 838 patients to placebo. The incidence of adverse events was higher in the frovatriptan-treated patients versus placebo (47% versus 34% respectively). However, the vast majority of the adverse events in both treatment groups were rated by the patients as mild or moderate in severity. The types of symptoms experienced by the patients taking frovatriptan was similar to those in the placebo group. The author concluded that frovatriptan was well tolerated by the patients regardless of their age, gender, race, concomitant medication, or the presence of cardiovascular risk factors.

In a separate study, also reviewed by Geraud et al.,[9] the tolerability and safety of frovatriptan 2.5mg was compared with sumatriptan 100 mg. This randomized, double-blind, parallel-group trial was conducted in various centers throughout Europe and in the United States. Nine hundred and sixty two patients were divided into two groups: 480 (49.9%) were assigned to receive frovatriptan 2.5 mg and 482 (50.1%) were assigned to receive sumatriptan 100mg. The study reported that significantly fewer patients experienced adverse events following frovatriptan than sumatriptan treatment (36% versus 43%). The total number of adverse events reported was approximately 50% higher in the patients who took sumatriptan (.91 events per patient) than in those who took frovatriptan (.62 events per patient). Three of the 480 patients who took frovatriptan 2.5 mg withdrew due to adverse events after attack 1 compared with 5 of the 482 sumatriptan treated patients. The author concluded that frovatriptan 2.5mg was better tolerated than sumatriptan 100mg.

Dosage and Administration

Frovatriptan is available as 2.5 mg tablets. The recommended dose is a single tablet of Frova® (frovatriptan 2.5 mg) taken orally. If the headache recurs after initial relief, a second tablet may be taken, providing that there is an interval of a least 2 hours between doses. The total daily dose of frovatriptan should not exceed 3 tablets (7.5 mg daily). There is no evidence that a second dose of frovatriptan is effective in patients who do not respond to a first dose of the drug for the same headache. The safety of treating an average of more than 4 migraine attacks in a 30-day period has not been established.[10]

Adverse Effects

The most common adverse effects associated with the use of frovatriptan at the recommended dose of 2.5mg were dizziness, dry mouth, chest pain, paresthesias, and flushing (Table 2). Other more serious reported adverse effects include cardiac failure; however, these events are extremely rare and most have been reported in patients with risk factors predictive of CAD. Events reported have included coronary artery vasospasm, transient myocardial ischemia, and ventricular fibrillation.[5]

Drug Interactions

There is a potential interaction between

Table 2. Adverse Effects Associated with Frovatriptan Use[9]

Common Adverse Effects	Frovatriptan (%)	Placebo (%)
Dizziness	8	5
Dry mouth	3	1
Paresthesia	4	2
Chest pain	2	1
Flushing	4	2
Hot or cold sensation	3	2

frovatriptan and other medications such as propranolol, moclobemide, ergotamine and/or fluvoxamine.[5] Since ergotamine is a potent central and peripheral vasoconstrictor, its coadministration with 5-HT agonists is generally not recommended due to the theoretical risk of additive vasoconstriction. On the other hand, fluvoxamine, a selective serotonin reuptake inhibitor (SSRI), and combined oral contraceptives are potent inhibitors of several CYP450 isoenzymes including CYP1A2; thus coadministration of these medications with frovatriptan should be avoided. This may result in weakness, hyperflexia, and incoordiation. Finally, since moclobemide selectively and reversibly inhibits MAO-A, it is contraindicated in patients receiving triptans.[5]

Cost

The mean retail price based on 3 community pharmacies for a blister card of 9 tablets of frovatriptan 2.5 mg is $142.88. The price range is between $140.99-$144.69.

Summary

The Food and Drug Administration (FDA) has approved Frova® (frovatriptan succinate) for the acute treatment of migraine attacks with or without aura in adults. Frovatriptan works by binding to and stimulating serotonin (5-HT) receptors causing vasoconstriction of human basilar arteries. It is well tolerated by patients regardless of their age, gender, race, concomitant medication, and/or presence of cardiovascular risk factors. Unlike other triptans, frovatriptan has a slow onset of action and long half-life (26 hours). Frovatriptan 2.5mg provides reliable and effective acute treatment for migraine and accompanying symptoms in adults.

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Lexapro® (escitalopram) is the pure S-enantiomer of the racemic derivative citalopram. It has recently been approved for the treatment of major depressive disorder. The initial adult dose is 10mg once daily. A fixed dose trial failed to demonstrate a greater benefit of 20mg over 10mg.

The indications for Prozac® (fluoxetine) have been expanded to include the treatment of panic disorder with or without agoraphobia and the long-term treatment of bulimia. Prior to this approval, the maximum treatment period for fluoxetine in the treatment of bulimia was 16 weeks.

Proton Pump Inhibitors in the Treatment of GERD: A Comparison

Tammy Calloway, Pharm.D. Candidate

Introduction

Gastroesophageal reflux disease (GERD) accounts for a variety of abnormalities in the esophageal mucosa and duodenum with gastric acid being central to the development of mucosal injury and resultant esophagitis. The degree and length of acid suppression are important factors in the management of GERD and duodenal ulcer. In GERD, for example, symptom severity correlates well with the degree of acid exposure. Therefore, the control of esophageal acidity remains the major therapeutic approach in the management of erosive esophagitis. Proton pump inhibitors (PPIs) are the most effective class of drugs for acid suppression.[2] Currently there are five PPIs on the market. Table 1 is a summary of their dosage forms and their FDA approved indications. This article will focus on comparing the pharmacology/pharmacokinetics, clinical trials, dosing, drug interactions, adverse effects and costs of the PPIs in the treatment of GERD.

Pharmacology/Pharmacokinetics

The PPIs belong to a class of drugs known as the substituted benzimidazoles and act by suppressing gastric acid secretion by specific inhibition of the H^+/K^+ ATPase, the proton pump, in the gastric parietal cell. The PPIs undergo acid-catalyzed conversion into active derivatives in the parietal cell, bind to cysteine residues on proton pumps, and inhibit acid production. These drugs block the final step of acid production. The degree of acid suppression appears to be dose related leading to inhibition of both basal and stimulated acid secretion irrespective of the stimulus.[1,15,17,18,19] With the possible exception of rabeprazole, the binding of PPIs to proton pumps is irreversible.[23] Therefore, the life of proton pumps along with the time required to produce more pumps are the primary factors controlling the duration of the pharmacodynamic effect of this class of drugs. Regeneration of proton pumps generally requires approximately 96 hours in humans.[9]

Pantoprazole differs from omeprazole and lansoprazole in that it binds to specific cysteine residues, which are believed to have a greater specificity for inhibition of the parietal cells, compared with other sites. This may be advantageous because many other tissues express proton pumps including the distal colon, kidney, biliary tract, vascular smooth muscle, and the heart, among others.[6] Pantoprazole is also more slowly activated at a moderately acidic pH (pH 4-6). In vitro chemical experiments at pH 5 have demonstrated that 20% of pantoprazole was activated after 1 hour, compared with 50% of lansoprazole and omeprazole. Slower activation at a moderately acidic pH may prevent unwanted effects on other tissues or cell organelles that express proton pumps. The clinical significance of these findings is unknown.[9]

Rabeprazole has a significantly quicker onset of acid inhibition than omeprazole, lansoprazole, and pantoprazole but not extent of acid inhibition. It also has a shorter duration of action because it dissociates from the ATPase enzyme more rapidly than the other PPIs.[12]

All PPIs undergo extensive hepatic metabolism and conjugation mainly through CYP2C19 and 3A4 isoenzymes of the cytochrome P450 enzyme system. They all are highly protein bound (95-98%).[1,15,17,18,19] The high pH-sensitive granules of omeprazole that dissolve only at pH 7 affects the bioavailability of the first oral dose which is 30% to 40% but rises with further doses. It should be taken 30 minutes prior to meals, preferably in the morning.[18] Lansoprazole also has high pH-sensitive granules and should also be administered 30 minutes prior to meals. The absolute bioavailability is 80%, which may be reduced by 50% if given after food.[17] Rabeprazole has an absolute bioavailability of 52%. Food delays the rate but not the extent of absorption, therefore rabeprazole can be administered without regard to meals.[1] Pantoprazole undergoes little first-pass metabolism resulting in an absolute bioavailability of 77%. Food delays the rate but not the extent of absorption, therefore pantoprazole can also be administered without regard to meals.[18] After a single dose of esomeprazole, the bioavailability is 64% and increases with repeated administration to 90%. Food

Table 1. FDA approved indications and dosage forms of the PPIs[7]

Product Name	Dosage Forms	Indications
Prilosec® (omeprazole)	Delayed-Release Capsules (10mg, 20mg, 40mg)	Active duodenal ulcer (DU), gastric ulcer (GU), GERD, maintenance of DU/GU, hypersecretory conditions.
Prevacid® (lansoprazole)	Delayed-Release Capsules and Suspension (15mg, 30mg)	Maintenance of DU/GU, gastric ulcer, NSAID-associated GU, GERD, erosive esophagitis, hypersecretory conditions.
Aciphex® (rabeprazole)	Delayed-Release Tablets (20mg)	GERD, GERD maintenance, duodenal ulcer, hypersecretory conditions.
Protonix® (pantoprazole)	Delayed-Release Tablets and Intravenous (40mg)	Erosive esophagitis with GERD.
Nexium® (esomeprazole)	Delayed-Release Capsules (20mg, 40mg)	Erosive esophagitis (EE), maintenance of (EE), GERD.

decreases the extent of absorption by 33-53%, therefore esomeprazole should be taken at least one hour before meals.[15]

Clinical Trials

The degree of acid suppression that is necessary for healing gastric acid disorders has not been well defined; however, maintaining the pH above 3 is believed to be an important objective for the healing of duodenal ulcers. The use of 24-hour intragastric pH monitoring is an accepted method for this assessment.[2] Most of the studies evaluate this method in determining the degree and length of acid suppression of each of the PPIs (Table 2).

In a double-blind, crossover study by Meyer and Meier[14], the effects on intragastric acidity was compared using low-dose omeprazole (10mg and 20mg) and lansoprazole 15mg in 12 healthy *H. pylori* negative subjects for 5 days. The authors concluded there was no significant difference between the intragastric acidity measurements and the time period above pH 4 for omeprazole and lansoprazole. Seensula et al.[22] noted similar reductions in 24-hour intragastric acidity with omeprazole and lansoprazole. This double-blind, randomized, crossover study involved 16 healthy volunteers who received either omeprazole 40mg or lansoprazole 60mg, with a washout period of at least 2 weeks between each treatment. Twenty-four hour intragastric acidity was measured at baseline and on day 5 of each treatment period. Median pH on day 5 for omeprazole 40mg was pH 4.15 and lansoprazole 60mg was pH 3.79. The authors concluded that omeprazole 40mg and lansoprazole 60mg had a similar effect on 24-hour intragastric acidity.

In a double-blind, crossover study, Hartmann et al.[2] compared the effect of pantoprazole 40mg and omeprazole 20mg on intragastric pH in 16 healthy subjects. Subjects underwent a 2 week washout period prior to crossover. The median 24-hour pH for pantoprazole 40mg was significantly higher than omeprazole 40mg, pH 3.15 vs. pH 2.05 ($p<0.01$). The authors stated that intragastric pH is a surrogate marker and does not necessarily correlate to clinical effect. Another study by Koop et al.[2], measured the effect of pantoprazole 40mg and omeprazole 40mg on intragastric pH of a 7 day regimen in 7 healthy volunteers. The intragastric pH was taken on the final day and measurements for pantoprazole and omeprazole were 4.2 and 4.0 respectively. Both pantoprazole and omeprazole displayed similar effects on intragastric pH.

Studies investigating esomeprazole with the other PPIs have all shown that esomeprazole provides significantly more effective acid control than the other PPIs when 24-hour intragastric pH was measured. However, the clinical relevance of these differences has not yet been defined.[2]

Data have shown that omeprazole 20mg daily is highly effective in the management of erosive esophagitis.[18] Studies with lansoprazole have reported a similar level efficacy and confirmed the role of the PPIs in the pharmacologic management of erosive esophagitis.[17] Table 3 summarizes the efficacy of short-term treatment using PPIs. Mee et al.[2] compared the healing rates of omeprazole and lansoprazole in 565 patients. Patients were random-

Table 2. Summary of Clinical Trials Using 24-hour Intragastric acid monitoring.

Author (N)	Study Design	Drugs Studied	Duration (Days)	Median 24-hr pH	% Time pH >4	P-value
Geus et al[8] (16)	R, IB, CO	Omeprazole 20mg qd Omeprazole 20mg bid Lansoprazole 30mg qd Lansoprazole 30mg bid	6	NA	53 78 46 70	<0.05 <0.05
Williams et al[2] (16)	R, DB, CO	Omeprazole 20mg qd Rabeprazole 20mg qd Placebo	8	4.2 4.7 1.5	NA	0.0001 vs placebo
Brunner et al[3] (12)	R, DB, CO	Omeprazole 40mg qd Pantoprazole 40mg qd	NA	NA	82.8 86.9	NA
Thomson et al[2] (28)	O, R, 2-way CO	Esomeprazole 40mg qd Lansoprazole 30mg qd	10	NA	57.2 51.8	<0.05
Wilder-Smith et al[2] (31)	O, R, 2-way CO	Esomeprazole 40mg qd Pantoprazole 40mg qd	5	4.7 3.7	66 44	0.001
Wilder-Smith et al[2] (23)	O, R, 2-way CO	Esomeprazole 40mg qd Rabeprazole 20mg qd	5	NA	61 45	0.005
Nexium & Prilosec Prescribing Information	R, DB, CO	Esomeprazole 20mg qd Omeprazole 20mg qd Esomeprazole 40mg qd Omeprazole 40mg qd	5 (N=38) 5 (N=114)	4.1 3.6	53 44 68 62	0.01 0.01

R=Randomized, IB=Investigator Blind, CO=Crossover, DB=Double-Blind, NA=Not Available

ized to either receive omeprazole 20mg daily or lansoprazole 30mg daily. Healing rates were assessed at 4 and 8 weeks. At week 4 omeprazole and lansoprazole had healing rates of 57% and 62% respectively. At week 8 the healing rate for omeprazole was 71% vs. 75% for lansoprazole. No significant differences were observed. Pilotto et al.[16] compared the efficacy of omeprazole, lansoprazole, and pantoprazole in 146 elderly patients with esophagitis diagnosed by endoscopy. Patients were randomized to receive omeprazole 20mg, lansoprazole 30mg, or pantoprazole 40mg daily for 8 weeks. Results showed complete healing of esophagitis in 83% (omeprazole), 88% (lansoprazole), and 92% (pantoprazole) of patients. The investigators concluded that all three are equally effective in healing esophagitis in elderly patients.

Esomeprazole has only been studied against omeprazole for the short-term treatment of gastric disorders. Richter et al.[20] compared the efficacy of esomeprazole 40mg to omeprazole 20mg daily. The study was a double-blind, randomized, US, multicenter study (n=2425), with *H. pylori* negative patients and photo documented erosive esophagitis. The primary endpoint was the number of patients healed at week 8. At week 4, healing rates were 81.7% with esomeprazole 40mg and 68.7% with omeprazole 20mg daily (p=0.001). Esomeprazole 40mg had an eight-week healing rate of 93.7% compared to 84.2% for omeprazole 20mg daily (p<0.001). The authors concluded that esomeprazole at week 4 has a similar healing rate as omeprazole at week 8. Esomeprazole showed significant clinical advantages over omeprazole in healing erosive esophagitis. However, esomeprazole 40mg has not been compared with omeprazole 40mg.

Omeprazole has recently received a patent extension from the FDA to look at its use in children and infants. There has been one randomized trial that compares ranitidine (Zantac®) with omeprazole in the treatment of children with refractory erosive esophagitis. Cucchiara et al. randomized 32 patients with refractory esophagitis, aged 6 months to 13 years, to receive either omeprazole 40 mg/1.72m^2 or high dose ranitidine (10 mg/kg) twice daily. All patients underwent 24-hour intraesophageal and intragastric pH monitoring and endoscopy

Table 3. Summary of Clinical Trials for the Short-term Treatment of GERD

Author (N)	Study Design	Drugs Studied	Remission Rates (%)	Duration	Comments
Castell et al[4,5] (1284)	R, DB, MC	Omeprazole 20mg (n=431) Lansoprazole 30mg (n=422) Lansoprazole 15mg (n=218) Placebo (n=213)	82[a]-91[a] 83[c]-91[c] 75[b]-79[b] 33-40	4 to 8 wks	OME was significantly better than LAN & placebo
Dekkers et al[2] (202)	R, DB, MC	Omeprazole 20mg (n=102) Rabeprazole 20mg + Placebo (n=100)	81-94 81-92	4 to 8 wks	Not significantly different
Corinaldesi et al[2] (208)	R, DB, MC, P	Omeprazole 20mg (n=105) Pantoprazole 40mg (n=103)	79-91 79-94	4 to 8 wks	Not significantly different
Kahrilas et al[2] (n=1960)	R, DB, MC, P	Omeprazole 20mg (n=650) Esomeprazole 20mg (n=656) Esomeprazole 40mg (n=654)	64.7-86.9 70.5[d]-89.9[e] 75.9[e]-94.1[e]	4 to 8 wks	EOME was significantly better than OME

R=Randomized, DB=Double-Blind, MC=Multicenter, P=Parallel, LAN=Lansoprazole, OME=Omeprazole, EOME=Esomeprazole
a= omeprazole vs. placebo and lansoprazole 15 mg ($p<0.05$), b= lansoprazole vs. placebo ($p<0.05$), c= lansoprazole 30 mg vs. placebo and lansoprazole 15 mg ($p<0.05$), d= esomeprazole 40 mg vs. omeprazole 20mg ($p<0.05$), e= esomeprazole 20 mg vs. omeprazole 20 mg ($p=0.09$)

with biopsy. Esophageal healing occurred in 9 of 12 (75%) of omeprazole treated children and in 8 of 13 (62%) of ranitidine treated children. These differences were not significantly different.[24] Other published information consists of case reports and series describing omeprazole use in pediatric patients refractory to conventional therapy. Gunasekaran and Hassall studied 15 children aged 10 months to 17 years who failed H2-receptor antagonist and prokinetic agents. Children 3 years of age and older were given omeprazole 20 mg in the morning, given in orange juice, cranberry juice, or yogurt. Children younger than 3 years where given omeprazole 10 mg in the same vehicles. Doses were adjusted until the esophageal pH was less than 4.0 for less than 6% of the time. The omeprazole dose required to control esophageal pH was 20-60 mg (0.7-3.3 mg/kg). The children received omeprazole treatment continuously for 5.5 to 26 months. All of the children where free of symptoms after 4-6 months of therapy. Nine of the patients underwent endoscopy all had esophageal healing.[24]

Dosing

Because of the chronic nature of GERD, long-term maintenance therapy is generally required. GERD relapse within 6-12 months has been reported in 50-80% of patients in whom antisecretory therapy was stopped. Long-term treatment with PPIs remains the method of choice for the medical treatment of severe GERD to maintain remission.[12] Patients requiring long-term therapy with PPIs will not develop tolerance to the PPIs.[6] Table 4 contains a summary of dosage and administration recommendations for the PPIs.

Dosing adjustments may be needed due to genetic polymorphism of CYP2C19, which results in slow or fast metabolizers. Omeprazole showed an increase in the AUC of approximately four-fold in Asian subjects compared to Caucasians.[18] This is less significant in the other PPIs. In patients with chronic hepatic disease, the bioavailability of the PPIs increases, reflecting decreased first pass effect, and/or an increase in the plasma half-life. Therefore, a dosage decrease may be warranted in this patient population, especially if long-term therapy is required. In the elderly population, clearance is decreased and the elimination half-life is increased but no accumulation is seen with the PPIs with once-a-day dosing, therefore no dosing adjustments are necessary. Since these drugs are not eliminated via the kidney as unchanged drug, no dosing adjustments are needed in renal impairment.[1,15,17,18,19]

Drug Interactions

Since all PPIs inhibit gastric acid secretion, they may decrease the absorption of drugs where gastric pH is an important determinant of bioavailability such as ketoconazole, itraconazole, ampicillin, and iron salts.[1,15,17,18,19] PPIs may also enhance the absorption of drugs where a higher pH facilitates absorption. Pantoprazole is the exception. It does not increase the absorption of digoxin. The

Table 4. Dosage and Administration for the PPIs[1,15,17,18,19]

PPI	Indication	Dose	Frequency
Prilosec® (omeprazole)	Active Duodenal Ulcer (DU)	20 mg qd	4 to 8 weeks
	Gastric Ulcer (GU)	40 mg qd	4 to 8 weeks
	GERD	20 mg qd	4 to 8 weeks
	Maintenance of DU/GU	20 mg qd	
	Hypersecretory Conditions	60-360 mg/d	>/= 5 years
Prevacid® (lansoprazole)	Maintenance of DU/GU	15 mg qd	
	Gastric Ulcer	30 mg qd	Up to 8 weeks
	NSAID-Associated GU	15 mg qd	Up to 12 weeks
	GERD	15 mg qd	Up to 8 weeks
	Erosive Esophagitis	30 mg qd	Up to 8 weeks
	Hypersecretory Conditions	60-120 mg/d	>/= 4 years
Aciphex® (rabeprazole)	GERD	20 mg qd	8 to 16 weeks
	GERD Maintenance	20 mg qd	
	Duodenal Ulcer	20 mg qd	4 weeks or longer
	Hypersecretory Conditions	60-120 mg/d	>/= 1 year
Protonix® (pantoprazole)	Erosive Esophagitis with GERD	40 mg qd	8 to 16 weeks
Nexium® (esomeprazole)	Erosive Esophagitis (EE)	20 - 40 mg qd	4 to 8 weeks
	Maintenance of (EE)	20 mg qd	
	GERD	20 mg qd	Up to 4 weeks

other PPIs likely increase the absorption of digoxin by decreasing the degradation by gastric acid. Antacids do not affect pantoprazole absorption but do decrease the absorption of lansoprazole.[9]

The differences in drug interactions among the PPIs lie in their difference in metabolism and effects on specific hepatic enzymes. Omeprazole and lansoprazole induce CYP1A4, though lansoprazole is considered a weaker inducer of this isoenzyme. Omeprazole and lansoprazole to a lesser extent are significant CYP2C9 inhibitors and weak CYP3A4 inhibitors.[17,18] Pantoprazole, rabeprazole, and esomeprazole have a lower potential for interactions with the cytochrome P450 enzyme system because of a lower affinity for the P450 enzymes.[13]

Adverse Effects

Short-term side effects of the PPIs are similar. The most commonly occurring short-term (<12 wks) adverse effects reported include headache, abdominal pain, diarrhea, constipation, nausea, and pruritis. Adverse effects associated with long-term (>12 wks) use are generally similar to those observed with short-term therapy. The suppression of gastric acid is dose-dependent among the PPIs and typically results in modest elevations of serum gastrin above pretreatment levels. However, only a small fraction of patients receiving PPI therapy will have serum gastrin concentrations above the normal range. Hypergastrinemia contributes to the development of gastric tumors, gastric cancer, colonic polyps, and gastric enterochromaffin cell hyperplasia. However, neither omeprazole nor lansoprazole has been associated with an increased risk of gastric cancer in patients receiving long-term therapy. Pantoprazole, rabeprazole, and esomeprazole are likely to have similar long-term safely profiles.[15,23]

Table 6. Monthly retail costs of the PPIs

PPI	Dose	Average (range)
Prilosec®	10 mg	$113.98 (104.02-123.95)
	20 mg	$122.37 (115.80-128.95)
	40 mg	$184.87 (171.07-197.95)
Prevacid®	15 mg	$120.95 (112.95-128.95)
	30 mg	$123.32 (113.70-132.95)
Aciphex®	20 mg	$121.83 (111.72-131.95)
Protonix®	20 mg	$105.00 (94.05-115.95)
	40 mg	$105.00 (94.05-115.95)
Nexium®	20 mg	$124.23 (115.51-132.95)
	40 mg	$124.23 (115.51-132.95)

Prices obtained from a retail chain store, discount source, and an internet pharmacy.

Cost

The costs of the different PPIs are summarized in Table 6.

Summary

Based on the superior efficacy profiles, PPIs are the drugs of choice in managing symptoms of GERD, healing and maintaining healing of duodenal and gastric ulcers, and treating hypersecretory conditions including Zollinger-Ellison syndrome. All of the PPIs provide similar efficacy rates in gastric acid disorders. The decision to select one PPI over the other is based on the agents' cost, formulations, FDA-labeled indications, and overall safety profiles. Intravenous or parenteral pantoprazole may be the preferred antisecretory agent for patients unable to take oral medications. Head to head studies comparing esomeprazole 40mg to omeprazole 20mg suggest that esomeprazole may be more effective or at least have a faster healing rate in patients with erosive esophagitis. However, studies have not been done comparing esomeprazole 40mg with omeprazole 40mg daily.

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