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Expert Opinion

Review of esomeprazole in the treatment of acid disorders

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Esomeprazole (Nexium™, AstraZeneca) is the *(S)*-isomer of omeprazole and the first proton pump inhibitor to be developed as an optical isomer. Esomeprazole has an improved pharmacokinetic profile, resulting in increased systemic exposure and less interindividual variability compared with omeprazole, and more effective suppression of gastric acid production compared with other proton pump inhibitors. In several large, double-blind, randomised trials, significantly higher rates of endoscopically-confirmed healing of erosive oesophagitis and resolution of heartburn have been achieved in patients with gastro-oesophageal reflux disease receiving 8 weeks of esomeprazole 40 mg o.d. compared with those receiving omeprazole 20 mg o.d. or lansoprazole 30 mg o.d. In the maintenance of healed erosive oesophagitis, esomeprazole 10, 20 or 40 mg o.d. was significantly more effective than placebo in two 6-month, randomised, double-blind trials. Additionally, esomeprazole 20 mg o.d. was more effective than lansoprazole 15 mg in the maintenance of healed erosive oesophagitis in another 6-month, randomised, double-blind trial. Healing of oesophagitis was also effectively maintained by esomeprazole 40 mg o.d. in a 12-month non-comparative trial. Esomeprazole 20 or 40 mg o.d. effectively relieved heartburn in patients with gastro-oesophageal reflux disease without oesophagitis in two 4-week, placebo-controlled trials. Clinical trials have shown that triple therapy with esomeprazole 40 mg o.d. in combination with amoxicillin and clarithromycin produced *Helicobacter pylori* eradication rates similar to those obtained using triple therapy involving twice-daily dosing with other proton pump inhibitors. Esomeprazole is well-tolerated, with a spectrum and incidence of adverse events similar to those associated with omeprazole.

Keywords: esomeprazole, gastro-oesophageal reflux, *Helicobacter pylori*, oesophagitis, peptic ulcer, proton pump inhibitor

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1. Overview of proton pump inhibitors in acid-related disorders

Gastro-oesophageal reflux disease (GERD) affects an estimated 19 million individuals in the US. In 2000, the direct and indirect costs for caring for patients with GERD amounted to ~ US$10.1 billion [1]. Moreover, the actual prevalence of the disease tends to be underestimated; in one survey, GERD was present but not diagnosed in 51% of patients seen in a general practice for unrelated conditions [2]. Complications of GERD include erosive oesophagitis, Barrett's oesophagus and adenocarcinoma [3]. The severity of disease and oesophageal damage does not correlate with the severity of GERD symptoms, resulting in difficulties in evaluating disease severity [4].

Proton pump inhibitors (PPIs) are commonly used in the treatment of patients with GERD or peptic ulcers. PPIs provide rapid, consistent symptom control and healing of erosive oesophagitis. PPIs are also used in the treatment of other acid-related disorders, such as Zollinger–Ellison syndrome [5], ulcer recurrence following long-term low-dose aspirin use [6], for prevention and healing of ulcers

in patients using NSAIDs [7], and for maintenance of healing of erosive oesophagitis [8,9]. Empiric PPI therapy is a practical method for diagnosing and treating patients with suspected GERD [10,11].

Most patients with GERD will require long-term management of their condition. There are two approaches to initial treatment of acid-related disorders. One approach involves starting treatment with the optimal dosage of the most effective agent, a PPI and 'stepping down' to a lower PPI dose or a less efficacious agent. The speed of symptom control in GERD patients with moderate or severe disease treated with initial PPI therapy provides both a diagnostic and therapeutic advantage that may ultimately result in lower direct costs [12]. Moreover, the safety, efficacy and cost-effectiveness of PPIs have made them the drug of choice in the long-term management of acid-related disorders [13,14]. Treatment with PPIs is associated with higher levels of patient satisfaction than treatment with H_2-receptor antagonists. The other approach involves starting treatment with minimum intervention and 'stepping up' to therapy with agents that have demonstrated more effectiveness. This option may result in initial treatment failure, resulting in additional office visits, prolongation of unnecessary episodes of discomforting heartburn, potential for disease progression and decreased quality of life (QoL) [15,16].

Although PPIs provide rapid and effective symptom control in patients with GERD, there is still room for improvement. In one survey published before esomeprazole was available, 42% of patients with heartburn treated with PPIs and 54% treated with H_2-receptor antagonists were not totally satisfied with the results [17], indicating that more effective pharmacotherapy was required. Omeprazole (Prilosec™, AstraZeneca), lansoprazole (Prevacid™, Takeda/TAP), pantoprazole (Protonix™, Atlanta/Wyeth), rabeprazole (AcipHex™, Eisai/Janssen), and esomeprazole (Nexium™, AstraZeneca) are the currently available PPIs. Esomeprazole is the most recent introduction into the PPI class.

2. Introduction to esomeprazole

The H^+/K^+-ATPase enzyme or 'proton pump,' is the final common pathway for gastric acid secretion in the stomach. Decreased secretion of hydrochloric acid by gastric parietal cells through inhibition of H^+/K^+-ATPase was first demonstrated for pyridylmethyl benzimidazole sulfides in the early 1970s. Subsequent modification of these agents to sulfoxides led to omeprazole, the first compound of this group to be used clinically for the management of disease associated with excessive gastric acid secretion and activity [18]. A number of substituted benzimidazole PPIs have since been developed, including lansoprazole, pantoprazole and rabeprazole. Esomeprazole, the *(S)*-isomer of omeprazole, is the first proton pump inhibitor to be developed as an optical isomer. Esomeprazole is optically stable in humans, with little inversion to the *(R)*-isomer [19], and was developed to improve the pharmacokinetic properties and acid-suppression characteristics of omeprazole. Systemic clearance is slower with the *(S)*-isomer (esomeprazole) than with the *(R)*-isomer or racemic omeprazole, resulting in a higher area under the plasma drug concentration versus time curve (AUC) with esomeprazole. The good correlation between AUC and acid suppression with esomeprazole [20] has translated into more effective symptom control and higher healing rates than with previously developed PPIs in three well-designed clinical trials [21-23].

3. Chemistry

The chemical name of esomeprazole is bis(5-methoxy-2-[*(S)*-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-yl) magnesium trihydrate. It has an empirical formula of $(C_{17}H_{18}N_3O_3S)_2Mg{\cdot}3H_2O$ and a molecular weight of 767.2 as the trihydrate or 713.1 as the anhydrous form [24]. The structural formula of esomeprazole is shown in Figure 1. The magnesium salt of esomeprazole is a white to slightly coloured crystalline powder that is slightly soluble in water. Without an enteric coating, esomeprazole magnesium rapidly degrades in acidic media, but has acceptable stability under alkaline conditions. *In vitro* studies have demonstrated that at a buffered pH of 6.8, the half-life of the magnesium salt is ~ 19 h at 25°C and ~ 8 h at 37°C. In the US, esomeprazole is available as delayed-release capsules for oral administration, each capsule containing 20 or 40 mg of esomeprazole in enteric-coated pellets. The pellets also contain glyceryl monostearate 40-50, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, methacrylic acid copolymer type C, polysorbate 80, sugar spheres, talc and triethyl citrate, as inactive ingredients. The capsule shells contain gelatin, FD&C Blue #1, FD&C Red #40, D&C Red #28, titanium oxide, shellac, ethyl alcohol, isopropyl alcohol, n-butyl alcohol, propylene glycol, sodium hydroxide, polyvinyl pyrrolidone and D&C Yellow #10 [24].

Outside of the US, esomeprazole is supplied as a 20 mg or 40 mg dispersible tablet (multiple unit pellet system [MUPS]).

4. Mechanism of action, pharmacokinetics and metabolism

4.1 Mechanism of action

Esomeprazole is a potent inhibitor of the final common pathway for gastric acid secretion by gastric parietal cells. A weak base, esomeprazole concentrates in the acidic compartment of the secretory canaliculus of the parietal cells where it undergoes an acid-catalysed transformation to a tetracyclic achiral cationic sulfenamide [24]. Inhibition of the H^+/K^+-ATPase enzyme occurs when the sulfenamide reacts with specific cysteines, blocking the final step in acid production and leading to adose-dependent reduction of gastric acid secretion. The binding of esomeprazole to the proton pump is covalent and irreversible [25,26].

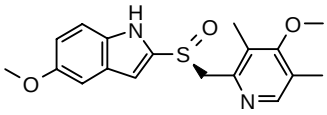

Figure 1. Chemical structure of esomeprazole.

4.2 Data in healthy volunteers

Esomeprazole is rapidly absorbed after oral administration. Peak concentration in plasma (C_{max}) is reached within 1 – 3.5 h after ingestion of 40 mg as enteric-coated pellets encapsulated in a hard gelatin capsule [27]. Dose-related increases in systemic exposure to esomeprazole occur after single doses, as demonstrated by AUC values. Of interest, repeated administration results in increased systemic exposure to esomeprazole. In two analyses involving a total of 32 healthy volunteers treated with a solution of esomeprazole 20 mg o.d., the mean AUC_{∞} on day 5 of dosing increased by 90% and C_{max} by 43% relative to day 1. Mean systemic bioavailability also increased, from 50 to 68% [27]. In the same study, systemic bioavailability of the esomeprazole capsule 40 mg o.d. increased with repeated once-daily dosing from 64% on day 1 to 89% on day 5, while C_{max} increased by 95% and AUC_{∞} by 159% over the same period [27].

Decreased first-pass metabolism and reductions in systemic clearance appear to be responsible for the increase in systemic exposure with esomeprazole. The mean AUC for the once-daily esomeprazole 20 mg capsule was 67% higher than that for omeprazole 20 mg at steady-state [20]. Esomeprazole is 97% bound to plasma proteins, which is similar to omeprazole and other PPIs [13,24,28-31]. Esomeprazole is extensively metabolised in the liver by the cytochrome P450 (CYP450) enzyme system to metabolites lacking antisecretory activity [32]. Of an oral dose administered as an aqueous solution ~ 80% is excreted as inactive metabolites and < 1% as active drug in the urine, with the balance eliminated as metabolites in the faeces [24,28]. Both optical isomers of omeprazole are converted primarily to hydroxy and 5-O-desmethyl metabolites by the CYP2C19 isoenzyme and to the sulfone metabolite by CYP3A4 [32]. However, *in vitro* studies indicate that the affinity of esomeprazole for the CYP2C19 isoenzyme is approximately tenfold that for CYP3A4. The rate of formation of the hydroxy metabolite is lower with esomeprazole and that of the sulfone and 5-O-desmethyl metabolites is higher, compared with *(R)*-omeprazole. The sum of the intrinsic clearance values for *in vitro* formation of the three major metabolites of *(R)*-omeprazole is three times that of the *(S)*-isomer, which predicts that esomeprazole would be cleared more slowly and would result in higher plasma concentrations – and greater systemic exposure – than racemic omeprazole [32]. Indeed, clinical studies confirmed this postulate. A proportion of the population (~ 3% of whites and 15 – 20% of Asians) do not express a functional form of CYP2C19 and are classified as 'poor metabolisers.' Dosage reductions are not considered necessary for such individuals because bio-equivalence data for esomeprazole indicate less than a twofold difference in AUC values between poor metabolisers and the rest of the population [18,24]. Following a single oral dose of rabeprazole, extensive metabolisers had a lower rabeprazole plasma concentration 3 – 4 h postdose, and less time above prespecified intragastric pH thresholds compared with poor metabolisers [33], indicating a possible need for higher doses of rabeprazole in these patients. A more recent study that evaluated intragastric pH following multiple doses of rabeprazole, omeprazole and lansoprazole in extensive metabolisers suggested that multiple dosing may ameliorate this effect [34]. With esomeprazole, there is less interindividual variability in AUC (versus omeprazole) in both extensive and poor metabolisers [28]. This property provided another reason for the clinical development of esomeprazole (P Lundberg, pers. comm., September 2002).

Esomeprazole capsules or MUPS should be swallowed whole, not chewed or crushed, once-daily, at least 1 h before meals [24]. Bioequivalence has been demonstrated for esomeprazole when administered either as an intact capsule or when the enteric-coated pellets from an opened capsule are mixed with one tablespoon of apple sauce and swallowed immediately [35]. This is advantageous for patients who have difficulty swallowing capsules. In addition, *in vitro* stability has been demonstrated for esomeprazole pellets suspended for 30 min in tap water, orange juice, apple juice, cultured (soured) milk or yoghurt [36]. An opened capsule of esomeprazole 40 mg suspended in water is also suitable for administration via a syringe into a nasogastric tube, yielding a bioavailability similar to that of oral administration of the intact 40 mg capsule [37]. This mode of delivery can be used with standard or small calibre nasogastric tubes or gastrostomy tubes [38].

4.3 Patients with GERD

Pharmacokinetic data from a double-blind, randomised, three-way crossover study in 36 patients with symptoms of GERD indicated that the pharmacokinetic profile of esomeprazole in patients with GERD is similar to that in healthy volunteers [39]. Patients were treated with oral esomeprazole 20 or 40 mg or omeprazole 20 mg o.d. for 5 days, with each treatment period separated by a washout period of at least 2 weeks. On day 5, C_{max} for both of the esomeprazole dosages was higher than that of omeprazole, although the T_{max} was similar (a median of ~ 1 h in each treatment group). Although the C_{max} appeared to increase proportionally with the dose of esomeprazole, there was a disproportionate increase in AUC. Notably, the geometric mean AUC for esomeprazole 20 and 40 mg was approximately twofold and over fivefold higher, respectively, compared with that for omeprazole 20 mg o.d. (Table 1). Interpatient variability in AUC was lower with esomeprazole than with omeprazole [39].

Table 1. Pharmacokinetic variables on day 5 of once-daily esomeprazole or omeprazole in patients with symptoms of GERD (adapted with permission from [39]).

Variable	Treatment group		
	Esomeprazole 20 mg	Esomeprazole 40 mg	Omeprazole 20 mg
Geometric mean AUC (μmol/h/l)	4.18*	12.64*	2.34
Median C_{max} (μmol/l)	2.42	5.13	1.41
Median $T_{½λz}$ (h)	1.3	1.6	1.0
Median T_{max} (h)	1.0	1.2	1.0
Interpatient variability in AUC	0.64	0.47	0.73

AUC: Area under the curve of plasma drug concentration versus time; C_{max}: Peak drug concentration in plasma; Interpatient variability in AUC: Standard deviation based on log-transformed values; $T_{½λz}$: Plasma terminal elimination half-life; T_{max}: Time to C_{max}.
*Significantly different versus omeprazole 20 mg, $p < 0.0001$.

4.4 Special populations

An understanding of the pharmacokinetics of this agent in patients with impaired hepatic function is important because esomeprazole is extensively metabolised by the liver. Mild or moderate hepatic impairment did not substantially alter the pharmacokinetic profile of esomeprazole 40 mg o.d. for 5 days in patients with cirrhosis of the liver [40]. In patients with severe disease (Child–Pugh class C), AUC values were ~ 2 – 3 times higher than in a control group of 36 patients with symptomatic GERD and normal hepatic function. Esomeprazole dosage adjustment is not necessary for patients with Child–Pugh class A or B hepatic insufficiency [40], but a maximum esomeprazole dose of 20 mg o.d. is recommended in patients with Child–Pugh class C hepatic insufficiency [24]. As < 1% of esomeprazole is excreted unchanged in the urine, the pharmacokinetic profile of esomeprazole in patients with renal impairment is unlikely to be altered relative to those in healthy volunteers [24].

5. Pharmacodynamics

5.1 Antisecretory activity

Maintenance of intragastric pH > 4 is critical to ensure symptom control and healing in patients with GERD [41]. Esomeprazole 40 mg, the recommended healing dose, suppresses intragastric acidity more effectively than the standard healing doses of rabeprazole (20 mg), lansoprazole (30 mg), pantoprazole (40 mg) or omeprazole (20 mg) when administered for 1 or 5 days (Table 2) [42-45]. The pharmacodynamic studies that compared esomeprazole with omeprazole, listed in Table 1, were conducted in healthy volunteers [44,46,47] or in patients with symptoms of GERD [39,42,44,45].

Esomeprazole 40 mg provided significantly faster suppression of gastric acid secretion than rabeprazole and lansoprazole in two comparative controlled investigations. In one study, the proportion of time with pH > 4 in the first 4 h after dosing on day 1 was 23.2% for esomeprazole 40 mg versus 11.0% for rabeprazole 20 mg ($p = 0.006$) [43]. In the other study, the proportion of time with pH > 4 in the first 24 h after dosing on day 1 was 40.6 versus 33.4% in esomeprazole 40 mg and lansoprazole 30 mg recipients, respectively ($p = 0.0182$) [48].

The pharmacodynamic effects of esomeprazole relative to other PPIs are strongly related to its pharmacokinetic properties. The higher AUC values for esomeprazole lead to increased drug delivery at the canalicular lumen and thus more pronounced inhibition of acid secretion, as demonstrated in the combined pharmacokinetic and pharmacodynamic studies by Lind *et al.* (Tables 1 and 2) [39].

5.2 Other pharmacodynamic effects

Chronic PPI use causes an increase in serum gastrin concentrations. The effect of esomeprazole on fasting serum gastrin levels was evaluated in a number of clinical trials lasting between 6 and 12 months [8,9,49]. The mean fasting gastrin level increased in the early weeks of treatment with esomeprazole in a dose-dependent fashion, then reached a plateau after 2 – 3 months of therapy. Serum gastrin levels decreased to baseline values within 4 weeks of discontinuation of therapy. In a study of 808 patients with erosive oesophagitis who received 12 months of maintenance treatment with esomeprazole 40 mg (twice the recommended dose), mean gastrin levels increased from baseline by 21.6 – 80.9 ng/l, with considerable intraindividual variability [49].

In rats, dose-related morphologic changes in the gastric mucosa, including enterochromaffin-like (ECL) cell hyperplasia and carcinoid tumours, have been observed in 24-month carcinogenicity studies of omeprazole [24]. In humans, the incidence of ECL cell hyperplasia increased with time in gastric biopsy specimens obtained from > 3000 patients receiving long-term omeprazole therapy [50]. However, neither ECL dysplasia nor carcinoid tumours of the gastric mucosa were observed in patients treated with omeprazole, nor did they occur in > 800 patients treated with esomeprazole 40 mg o.d. for ≤ 12 months [49].

Esomeprazole given orally at doses of 20 or 40 mg for 4 weeks has no apparent effect on thyroid function and, based on omeprazole studies, esomeprazole is expected to have no effect on carbohydrate metabolism or circulating levels of parathyroid

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