Esomeprazole: a new proton pump inhibitor for NSAID-associated peptic ulcers and dyspepsia

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Ulcer and ulcer symptoms related to the use of non-steroidal anti-inflammatory drugs (NSAIDs) and aspirin constitute a major global health issue. Despite various attempts to prevent and heal injuries inflicted by NSAIDs and aspirin, acid suppression remains one of the cornerstones in the management of NSAID-associated ulcers. Esomeprazole, the S-optical isomer (enantiomer) of omeprazole, suppresses gastric acid secretion by inhibiting the parietal cell membrane enzyme H+/K+-ATPase. With improved bioavailability, due to reduced first-pass metabolism in the liver, esomeprazole promises to be more potent in acid suppression in the stomach. Similar to omeprazole, the safety profile of esomeprazole has been well established. Clinical studies comparing esomeprazole with other proton pump inhibitors (PPIs) in the healing of NSAID-related ulcer are few. Recent multicenter randomized studies demonstrated that esomeprazole significantly improves dyspeptic symptoms in patients taking nonselective NSAIDs and specific cyclooxygenase-2 inhibitors. Esomeprazole also protects the stomach from aspirin-induced ulcer bleeding. Safety profiles of esomeprazole appear promising.

Non-steroidal anti-inflammatory drugs (NSAIDs) are the most commonly used medications for chronic pain and arthritis due to their efficacy in pain control. However, it is well recognized that NSAIDs cause various gastrointestinal (GI) conditions including dyspepsia, peptic ulcer disease and its complications (bleeding and perforation), and small bowel stricture. These complications have a huge impact on healthcare system around the world. In the USA alone, the use of NSAIDs causes more than 100,000 hospitalizations and 17,000 deaths annually [1]. The risk is substantially higher among the elderly population and those with concomitant medical illnesses.

As mucosal injury induced by NSAIDs is an acid-dependent process, effective acid suppression is one of the ways to prevent NSAID-associated ulcer formation and complications. Proton pump inhibitors (PPIs) are a group of acid-suppressing agents that act by binding covalently to the amino acid cysteine 813 residue present at their primary binding site on the H+/K+-ATPase, also known as the ‘proton pump’, on the luminal surface of gastric parietal cells [2]. This results in irreversible inhibition of acid secretion by the gastric H+/K+-ATPase. Only after recruiting newly synthesized proton pump molecules from the Golgi apparatus of the cell will acid secretion gradually resume [3]. As PPIs block the final step in the pathway to gastric acid secretion arising from various stimuli, they are effective against both basal and stimulated acid secretion. PPIs are most effective against meal-induced gastric acid secretion [3]. Omeprazole, the first drug in this class, was introduced in 1988. Since then, three other PPIs have been introduced: lansoprazole (1995), rabeprazole (1999) and pantoprazole (2000). In 2001, esomeprazole was introduced as the S-optical isomer of the racemic molecule of omeprazole. All PPIs share a common structural motif but vary in their substitutions. PPIs have revolutionized the management of acute upper gastrointestinal bleeding (GIB), as adequate acid suppression improves the success of endoscopic hemostasis, and reduces the need of surgery [4]. This article focuses on the existing literature of esomeprazole and its effects in preventing and healing of NSAID-induced GI mucosal injury.

Chemistry
Omeprazole is a racemate with a sulfur atom which acts as a chiral center for the compound. It contains two optical isomers, S- and R-omeprazole. Conversion of the two enantiomers to the active form, the achiral sulfenamide, occurs via an acid-dependent chemical reaction at the luminal surface of the parietal cells and at the same rate for both enantiomers.

Esomeprazole is the S-isomer (enantiomer) of omeprazole, and the first PPI to be developed as an optical isomer. Similar to other PPIs, esomeprazole suppresses gastric acid secretion by inhibiting the parietal cell membrane enzyme...
H⁺/K⁺-ATPase. Esomeprazole is rapidly degraded in acidic media but is stable under alkaline conditions just as all other PPIs are. Each capsule of esomeprazole magnesium contains enteric-coated granules to prevent esomeprazole degradation by gastric acidity.

Esomeprazole, chemical name: (S)-5-methoxy-2-([(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl)-1H-benzimidazole, (Figure 1) is a weak base. It is converted to its active form, a sulfenamide analog, in the acidic environment of the gastric parietal cell. It effectively blocks acid secretion by irreversibly binding to and inhibiting the enzyme H⁺/K⁺-ATPase that resides on the luminal surface of the parietal cell membrane, resulting in disulfide bond formation with cysteine 813 located within the α-subunit of the enzyme (Figure 2). This is the residue that is intimately involved in H⁺ transport. All PPIs are weak protonatable pyridines, with a pKa 4.0 for

Figure 1. Molecular structure of omeprazole: (S)-5-methoxy-2-([(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl)-1H-benzimidazole and its two optical isomers, the S-isomer (esomeprazole) and the R-isomer of omeprazole.
omeprazole, esomeprazole and lansoprazole, 3.9 for pantoprazole and 5.0 for rabeprazole. The rate of conversion varies among the compounds and is inversely proportional to their pKa: that is, rabeprazole > omeprazole/esomeprazole = lansoprazole > pantoprazole. As a result, they accumulate specifically and selectively in the secretory canaliculus, the highly acidic space, of the parietal cell [3]. Within that space, PPIs undergo an acid catalyzed conversion to become a reactive species, the thiophilic sulfenamide, which are permanent cations.

Pharmacology
Esomeprazole has a different pharmacodynamic and pharmacokinetic profile from its parent compound, omeprazole. It is designed to improve bioavailability of the drug with more consistent pharmacokinetics and hence better acid control. After ingestion, both the S- and R-isomers of omeprazole are absorbed through the intestine and passed through the liver (first-pass metabolism) and transformed into the active compound which is delivered back to the stomach as two inactive metabolites, the 5-hydroxy and sulfone forms of the compounds [5]. Unlike the R-isomer which is predominantly metabolized by CYP2C19 (98%), S-isomer (esomeprazole) is metabolized by both CYP2C19 (73%) and CYP3A4 (27%).

As a result of this difference in liver metabolism of the drug, intrinsic clearance of R-isomer is three times faster than the S-isomer, hence a higher plasma concentration of the later. In contrast, esomeprazole has reduced first-pass metabolism and slower clearance.

Pharmacokinetic studies show that esomeprazole has a significantly higher area under curve (AUC) value and longer half-life than both the R-isomer and racemic omeprazole, resulting in a 10–20% increase in the acid-suppressing effect of the drug [6]. The half-life of elimination is 1–1.5 h, and the time to reach peak plasma drug level after oral administration is 1.5 h. Although altered P450 metabolism appears beneficial as it achieves a higher plasma levels of esomeprazole, when the CYP2C19 pathway becomes saturated, the isoenzyme may become a major target for interactions with other drugs, including warfarin, diazepam and phenytoin. CYP3A4-mediated metabolism may also be activated under such conditions and hence become the principal route of drug elimination. Furthermore, induction of CYP450A, another P450 isoenzyme, may occur in CYP2C19-deficient or saturated individuals, making them susceptible to interference with theophylline metabolism [5].
Absorption of esomeprazole is decreased by 43–53% when taken with food. As the amount of H+/K+-ATPase present in the parietal cell is greatest after prolonged fasting, PPIs are best administered before meals. In most individuals, once-daily dosing is sufficient to produce the desired level of acid inhibition. A second dose, if deemed necessary, should be administered before the evening meal.

Pharmacodynamic studies have shown that the daily oral administration of esomeprazole 40 mg is significantly more effective than that of omeprazole 20 or 40 mg, lansoprazole 30 mg, rabeprazole 20 mg and pantoprazole 40 mg in controlling intragastric acidity during single and repeated daily dosing (Figure 3) [7,8]. Esomeprazole 20 and 40 mg maintained the intragastric pH at above 4 for a mean of 12.7 and 16.8 h, respectively, compared with 10.5 h with omeprazole 20 mg [9]. The median 24 h intragastric pH achieved with esomeprazole 20 mg (pH = 4.1) and 40 mg (pH = 4.9) were also significantly higher than that with omeprazole 20 mg (pH = 3.6). Furthermore, interpatient variability in intragastric pH and the AUC was consistently less with esomeprazole than omeprazole [9]. Two studies performed in 52 healthy individuals showed that esomeprazole 40 mg was significantly more effective than lansoprazole 30 mg for controlling intragastric acidity, with a difference in percentage of time where gastric pH was above 4 of 5.5% (95% confidence interval [CI]: 1.8–9.1%) [10] and 12.4% CI: 7.4–17.5% [11]. The proportion of individuals with gastric pH controlled above 4 for more than 12 or 16 h was higher with esomeprazole [10].

PPIs should not be given concomitantly with histamine-2 receptor antagonists (H2RAs), prostaglandins, or other antisecretory agents due to the marked reduction in their acid inhibitory effects when administered with these drugs simultaneously [2,3]. These findings are based on the pharmacokinetic property of esomeprazole, which is converted to its active form in the acidic environment. It is recommended that a H2RA can be used with a PPI, provided there is a sufficient time interval between administrations of the two-acid suppressing agents (but the precise minimal time interval has not been established). For example, H2RA can be taken before bed time by individuals who report nocturnal acid breakthrough after taking a PPI in the morning [12]. Nonetheless, there has not been any pharmacokinetic or clinical trial to validate this recommendation.

**Figure 3. Percentages of times with a mean intragastric pH of more than 4 after daily oral administration of drug.**

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<thead>
<tr>
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<tr>
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<td>A vs D</td>
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<td>A vs C</td>
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Esomeprazole 40 mg (A), omeprazole 20 mg (O20) or 40 mg (O40), lansoprazole 30 mg (B), rabeprazole 20 mg (C) and pantoprazole 40 mg (D) during single and repeated daily dosing in five separate studies in symptomatic GERD patients, on day 1 and day 5 [7,8]
In elderly patients and patients with mild-to-moderate hepatic dysfunction (Child-Pugh classification A or B), the pharmacokinetics of esomeprazole are not altered \[13,14\]. However, patients with severe hepatic impairment (Child-Pugh Class C) have a significantly prolonged half-life and increased AUC of esomeprazole \[13\], therefore such patients should not take esomeprazole in excess of 20 mg/day \[2\]. Conversely, no dose adjustment is necessary in renal impaired patients, as the pharmacokinetics of esomeprazole in individuals with impaired renal function is similar to that in healthy individuals \[15\].

Clinical efficacy of esomeprazole in NSAID-associated ulcers

NSAIDs cause gastroduodenal injuries by their inhibitory effect on prostaglandin synthesis, together with topical injury and neutrophil-mediated injury \[16\]. The acidic environment in the stomach and proximal duodenum exacerbates NSAID injury by disrupting the basement membrane \[17\], affecting platelet aggregation \[18\] and impairing ulcer healing \[19\]. Therefore acid suppression has been one of the cornerstones in the treatment of NSAID-associated ulcers. While there are many studies investigating the uses of esomeprazole in gastroesophageal reflux disease (GERD) and Helicobacter pylori infection, relatively few clinical trials have focused on the use of esomeprazole in NSAID-associated ulcers.

Healing NSAID-related ulcers

Similar to other PPIs, esomeprazole is more effective than H2RAs for the treatment of NSAID-associated gastroduodenal ulcers \[20,21\]. In a recently published multicenter, double-blind randomized trial including 406 nonselective NSAID or selective cyclooxygenase (COX)-2 users who had gastric ulcers, a single daily dose of esomeprazole 40 or 20 mg was more effective than ranitidine 150 mg twice daily for the healing of ulcers. At week 8, gastric ulcer (GU) healing rates with esomeprazole 40 mg, esomeprazole 20 mg and ranitidine were 91.5% (118/129; 95% CI: 86.7–96.3%), 88.4% (122/138; 95% CI: 83.1–93.7%) and 74.2% (98/132; 95% CI: 66.8–81.7%), respectively (p < 0.01 for both comparisons) \[22\]. Peptic ulcer healing is similar when using standard doses of any of the PPIs. No single PPI has been studied at a comparable dose head-to-head with other agents within the class in the healing of NSAID-related ulcers.

It has been proposed that NSAIDs induce mucosal injury by increasing the number of free radicals and reducing antioxidants in the mucosa. One recent study examined the healing mechanisms of esomeprazole in the treatment of NSAID-related gastropathy \[23\]. A/J mice received saline, indomethacin, esomeprazole or indomethacin and esomeprazole and were sacrificed and measured for total gastric antioxidant. It was shown that esomeprazole increases gastric total antioxidant capacity in mice. Lower mortality (0 vs 38%, p = 0.05) was found in mice receiving esomeprazole and indomethacin than indomethacin alone. The mechanism of PPI in healing NSAID-induced mucosal injury is likely to be more complicated than simple acid suppression.

Prevention of NSAID-related ulcers or upper gastrointestinal symptoms

Efficacy of esomeprazole in the prevention of NSAIDs – (both nonselective and COX-2-selective) associated ulcers has been assessed in a retrospective study of 1429 patients \[24\]. It was found that esomeprazole given at doses of 20 and 40 mg daily was associated with statistically significant lower rates of endoscopic gastroduodenal ulcers (absolute risk reduction (ARR) = 11.8% and 12.4% respectively) compared with placebo in patients taking nonselective or COX-2-selective NSAIDs. Nonetheless this study used endoscopic ulcers instead of clinical events as an end point. Further studies on clinically relevant outcomes would be worthwhile.

Two recent multinational, multicenter double-blind studies (NASA1 and SPACE1) were designed to study symptom improvement with esomeprazole compared with placebo in patients taking NSAIDs, including COX-2 inhibitors \[25\]. These two studies enrolled a total of 1642 NSAID users with no history of gastroduodenal ulcers, erosive esophagitis, and H. pylori infection. The primary measurement was the patient-reported change in the upper GI symptom (pain, discomfort or burning in the upper abdomen) score on a severity scale (0–6) from the 7 days prior to treatment to the last 7 days in the study. Among these 1624 patients, 1164 who had symptoms of at least moderate severity (score of 3 or more) on at least 3 of the final 7 days of the run-in period, were randomized to receive 4 weeks of either esomeprazole 20 mg, esomeprazole 40 mg, or placebo once daily. The proportion of patients taking only selective COX-2 inhibitors was 30 and 38% in NASA1 and SPACE1, respectively. In both
studies, esomeprazole was found to be associated with significant symptom improvement compared with placebo (p < 0.001), while the two regimens (esomeprazole 20 or 40 mg once-daily) had similar effects (Table 1). When the results of two studies are pooled together, the symptom score improvements were 2.25 with esomeprazole 20 mg and 2.07 with esomeprazole 40 mg versus 1.61 with placebo for nonselective NSAID users. Among those who received selective COX-2 inhibitors, symptom improvement was 2.20, 2.07 and 1.64 for esomeprazole 20 mg, esomeprazole 40 mg and placebo respectively (Figure 4) [25]. The authors conclude that esomeprazole at both 20 and 40 mg doses improve upper GI symptoms for non-selective NSAID and selective COX-2 inhibitors. This is of note that in NASA1 and SPACE1, 58.7 and 78.5% of patients reported moderate or severe heartburn respectively. Individual symptom analyses showed that heartburn or acid reflux improved most after esomeprazole. Therefore the effective symptom improvement in patients taking NSAIDs by esomeprazole was at least partly contributed by its efficacy in controlling acid reflux.

*Helicobacter pylori* & NSAID-related ulcers

Eradication of *H. pylori* reduces the risk of NSAID-associated ulcers in initially NSAID-naive patients. The protective effects of *H. pylori* eradication in patients who have not been taking NSAID but are about to start the medication was demonstrated in two randomized study [26,27]. Conversely, high-risk patients who had history of NSAID-induced ulcer bleeding may not be sufficiently protected by *H. pylori* eradication alone. With established NSAID users who present with ulcer complications and *H. pylori* infection, curing *H. pylori* infection should be accompanied by coprescription of esomeprazole or other PPI and antibiotics [28].

A 1-week regimen of esomeprazole-based triple therapy is as effective as omeprazole-based therapy in two randomized double-blind trials studying the treatment of *H. pylori* infection [29,30]. Esomeprazole at a dose of 20 mg twice-daily with amoxycillin 1000 mg twice-daily and clarithromycin 500 mg twice-daily for 7 days would be sufficient to achieve a successful eradication of *H. pylori* in 86–88% of cases.

Aspirin was known to increase the risk of upper GIB by at least 2-fold even at low doses [31]. PPIs reduce the risk of aspirin-induced ulcer bleeding [28,32]. Coprescribing PPIs for patients at high risk for ulcer bleeding who are taking aspirin has been advocated [33,34]. *H. pylori* eradication may further reduce the risk of ulcer recurrence in patients on aspirin [28]. However, treatment of such patients with a PPI in addition to the eradication of *H. pylori* can significantly reduce the risk of recurrent ulcer complications [32].

Currently the American College of Cardiology-American Heart Association guidelines recommend using clopidogrel for patients who have a history of major GI intolerance for aspirin. In a recent randomized control trial clopidogrel was compared with low-dose aspirin combined with esomeprazole for clinical ulcer symptoms and complications. The cumulative incidence of recurrent bleeding during the 12-month period was 8.6% (4.1–13.1%) among patients who received clopidogrel and 0.7% (0–2.0%) among those who received aspirin plus esomeprazole (ARR 7.9%; 95% CI: 3.4–12.4%). Aspirin plus esomeprazole appears to be superior to
clopidogrel in the prevention of ulcer complications at least in high-risk patients. PPI with low-dose aspirin may offer a safer and cheaper option for patients with coronary heart disease that requires antiplatelet therapy [35].

**Maintenance therapy**

In general, maintenance therapy should be considered to prevent recurrence in high-risk patients, those with a history of complications, frequent recurrences, refractory, giant, or severely fibrosed ulcers. In such patients who are also infected with *H. pylori*, maintenance therapy should be continued at least until cure of the infection has been confirmed, and possibly longer. Long-term maintenance therapy is clearly indicated in high-risk patients who fail to achieve *H. pylori* eradication or who have *H. pylori*-negative ulcers [36].

Esomeprazole was also demonstrated to be an effective maintenance therapy in peptic ulcer diseases. Development of endoscopic gastric or duodenal ulcers was significantly reduced in NSAID users taking esomeprazole 20 mg (5.2%) or 40 mg (4.6%) versus placebo (17.0%), who were at risk of developing ulcers, as they were old 60 years of age or older or had a history of gastroduodenal ulcers [37].

**Intravenous esomeprazole**

NSAID-associated ulcers occasionally presented as acute upper gastrointestinal bleeding. Effective acid suppression, especially in the initial 24 h, optimizes clot stability and reduces the ulcer rebleeding rate after endoscopic therapy [38]. It was found that the ulcer rebleeding rate is reduced by effective and constant control of intragastric pH [39]. This continuous suppression of acid secretion can only be reliably achieved by a bolus injection followed by continuous intravenous infusion of PPI [40], in view of their relatively short. High-dose intravenous esomeprazole in combination with endoscopic therapy substantially reduced the risk for recurrent GIB, repeated endoscopic therapy, frequency of blood transfusion, and duration of hospitalization [4]. Combination of endoscopic therapy and omeprazole infusion is also superior to omeprazole infusion alone for preventing recurrent bleeding from ulcers with nonbleeding visible vessels and adherent clots [41]. It has been shown in healthy volunteers that intravenous esomeprazole provided faster and more effective gastric acid control than intravenous pantoprazole (40 mg once-daily for 5 days) [42]. Theoretically, intravenous esomeprazole should be at least as effective as intravenous pantoprazole in upper GIB. To date, there is no clinical trial investigating the combination of intravenous esomeprazole and endoscopic hemostasis in the treatment of ulcer bleeding. A prospective double-blind randomized trial to investigate the role of intravenous esomeprazole is very much in need.

Intravenous and oral esomeprazole (20 or 40 mg) has been studied in two trials involving 64 healthy volunteers [43]. No significant differences were found between the two different routes of administration of esomeprazole with respect to the amount of time mean intragastric pH remained greater than 4 throughout day 1 or day 5 of treatment in the 40 and the 20 mg study (Table 2). Control of intragastric acidity on day 1 is much faster with intravenous than oral esomeprazole. This could be important as most clinical rebleeding occurs within the first day.

**Safety & tolerability**

As a class, PPIs are extremely safe. However, differences in their metabolism may lead to specific drug interactions. The long-term safety of these drugs has been best established with omeprazole since it was the first to become clinically

### Table 1. Symptom improvement of NASA1 and SPACE1 studies [25].

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<tr>
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<td>2.35 ± 1.70</td>
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<td>1.55 ± 1.19</td>
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<tr>
<td>Selective COX-2 inhibitor users</td>
<td>1.64 ± 1.46</td>
<td>2.21 ± 1.46</td>
<td>1.92 ± 1.38</td>
<td>1.58 ± 1.37</td>
<td>2.20 ± 1.26</td>
<td>2.24 ± 1.62</td>
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</tbody>
</table>

available. These data suggest that its use for more than 15 years has been safe [44]. The common adverse events in clinical trials associated with the use of esomeprazole, including headache, abdominal pain, diarrhea, flatulence, nausea, vomiting and constipation are not dose-related. In general, the safety profile of esomeprazole is similar to that of other PPIs [45]. Esomeprazole has been classified as Class B in pregnancy use. No teratogenic effect has been observed in animal studies. Esomeprazole is excreted in breast milk, therefore it should not be recommended to breast-feeding women. In one study, 113 pregnant women exposed to omeprazole during pregnancy were compared with controls exposed to known nonteratogens and with women who took H2RAs during pregnancy [46]. Birth weight, gestational age at delivery, preterm deliveries and neonatal complications were comparable among the three groups. A population-based, case-control study involving 3236 births found that first trimester exposure to cimetidine, omeprazole, or ranitidine was not associated with an increased risk of congenital malformations, preterm delivery or growth retardation [47]. Nevertheless it is of note that the long-term safety data are largely from studies on GERD. NSAID users are older and more likely to have comorbid, illness thus the safety profile in this population might be different.

Use of esomeprazole is contraindicated in patients with previous hypersensitivity to the drug. Other PPIs should be considered in such circumstances. Overdose may lead to confusion, drowsiness, blurred vision, tachycardia, nausea, sweating, headache or dry mouth. Treatment is symptom-directed and supportive, as esomeprazole is not dialyzable.

**Expert commentary**

Esomeprazole, the $S$-isomer of omeprazole, has pharmacokinetic properties that may make it more effective than omeprazole in acid suppression. Esomeprazole maintains intragastric pH at a higher level for a longer period than other PPIs. Esomeprazole is more effective than H2RAs in healing NSAID-associated ulcers. It is also effective as part of the eradication therapy of *H. pylori*, and preventive or maintenance therapy of peptic ulcers. Its effectiveness in NSAID-associated upper GI symptoms can be partly contributed to its efficacy in controlling acid reflux and heartburn, similar to its efficacy in GERD patients.

**Outlook**

With the aging population and increasing consumption of NSAIDs and COX-2 inhibitors, upper GI symptoms related to the use of these medications is likely to increase. Esomeprazole

| Table 2. The amounts of times with mean intragastric pH > 4 throughout day 1 or day 5 of intravenous versus oral treatment of esomeprazole (20 or 40 mg) in 64 healthy volunteers [36]. |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
|                                 | Esomeprazole 20mg               |                                 | Esomeprazole 40mg               |
|                                 | Day 1 (h)                       | Day 5 (h)                       | Day 1 (h)                       | Day 5 (h)                       |
| Intravenous                     | 7.3                             | 11.9                            | 10.1                            | 15.9                            |
| Oral                            | 6.6                             | 12.3                            | 8.8                             | 15.3                            |

**Highlights**

- Use of nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, is a common cause of gastrointestinal bleeding, resulting in significant morbidity and mortality.
- Esomeprazole, the $S$-optical isomer (enantiomer) of omeprazole, suppresses gastric acid secretion by inhibiting the parietal cell membrane enzyme H+/K+-ATPase.
- Esomeprazole has a reduced first-pass metabolism and a lower clearance rate compared with omeprazole, resulting in a longer half-life and increased duration of raised intragastric pH to over 4.
- While there are many studies investigating the uses of esomeprazole in gastroesophageal reflux disease and *H. pylori* infection, relatively few clinical trials focus on the use of esomeprazole in NSAID-associated ulcers.
- Esomeprazole significantly improves the symptoms in patients taking nonselective NSAIDs as well as specific COX-2 inhibitors at both 20 and 40 mg single doses.
- A 1-week regimen of esomeprazole-based triple therapy is as effective as omeprazole-based therapy in curing *H. pylori* infection.
- Aspirin plus esomeprazole has been shown to be superior to clopidogrel in the prevention of recurrent ulcer bleeding.
- The clinical efficacy of intravenous esomeprazole in preventing recurrent bleeding from ulcers with high-risk stigmata of recent hemorrhage warrants further study.
will continue to play an important role in protecting the upper GI tract against NSAIDs and COX-2 inhibitors related to ulcer and dyspepsia. To date, head-to-head comparisons of esomeprazole to omeprazole and other PPIs in the management of NSAID- or aspirin-related ulcer and ulcer complications are not available. Future studies in these areas are warranted.

**Bibliography**

Papers of special note have been highlighted as of interest (*) or of considerable interest (**) to readers.


**Showed that a high-dose infusion of esomeprazole substantially reduces the risk of recurrent bleeding after endoscopic treatment of bleeding peptic ulcers.**


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** Showed that the eradication of H. pylori is equivalent to treatment with omeprazole in preventing recurrent bleeding in aspirin users, while omeprazole is superior to the eradication of H. pylori in preventing recurrent bleeding in patients who are taking other NSAIDs.


** Showed that aspirin plus esomeprazole was superior to clopidogrel in the prevention of recurrent ulcer bleeding in patients who have a history of aspirin-induced ulcer bleeding.


** Showed that the incidence of H. pylori-negative idiopathic bleeding ulcers is rising and these ulcers are prone to recurrent complications.


** Showed that the combination of endoscopic therapy and omeprazole infusion is superior to omeprazole infusion alone for preventing recurrent bleeding from ulcers with nonbleeding visible vessels and adherent clots.


** Showed that intravenous esomeprazole provides similar levels but faster control of intragastric acid on both day 1 and day 5 of treatment compared with oral administration.


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<tr>
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