Intravenous Proton Pump Inhibitors

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Intravenous (IV) administration of a proton pump inhibitor (PPI) is a faster way to achieve gastric acid suppression than oral administration of the same agent. Peak suppression after IV administration occurs within hours, compared with several days later after oral administration. Thus the IV route of administration offers a faster onset of gastric suppression, achievement of intragastric pH closer to neutrality, and better bioavailability. The PPIs that have IV formulations in the United States (esomeprazole, lansoprazole, and pantoprazole) are approved for different indications; the key differences among them relate to their ability to reach specific gastric pH, time to maintain a specific gastric pH, and ease of use of the IV formulation (eg, reconstitution, requirement of inline filters, infusion times).

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Key words: Proton pump inhibitors • Esomeprazole • Lansoprazole • Pantoprazole • Intravenous administration • Pharmacology • Gastroesophageal reflux disease
Intravenous PPIs

This article will focus on comparing the PPIs that have IV formulations in the United States: esomeprazole, lansoprazole, and pantoprazole.

Clinical Pharmacology

All of the PPIs are prodrugs and require acidic activation to be effective. The oral formulations of PPIs are all acid labile and need to be protected from premature activation. So the drug is usually protected by the use of an enteric coat around the tablets or by filling the capsules with enteric-coated granules. When the unprotonated prodrug is released in the small intestine, it is rapidly absorbed. Once the orally administered PPI is absorbed, it is activated and handled just like the intravenously administered PPI. To be activated, the PPI must penetrate the cell membrane and enter into the parietal cell. The PPI is then transported across the canalicul ar membrane into the canaliculus space, where it is protonated and thereby trapped in the secretory canaliculus of the parietal cell and becomes the active moiety that can bind to cysteine residues within the (H⁺/K⁺)-adenosine triphosphatase (ATPase) enzyme, resulting in inhibition of gastric acid secretion. The exception to this binding is pantoprazole, which forms a covalent bond to 2 sites (cysteine residue 813 and 822) of the (H⁺, K⁺)-ATPase enzyme system.

The IV formulation improves the systemic bioavailability of PPIs because the acidity of the stomach and the upper duodenum and drug lability in this environment are avoided. Thus more drug is delivered to the site of action during the first few days of therapy.

Pharmacokinetics

Esomeprazole

In studies comparing the oral and IV administration of esomeprazole, IV administration was associated with a twofold higher peak concentration and a 66% to 83% greater area under the plasma concentration-time curve compared with oral administration of the same single dose. Differences were similar but slightly less pronounced after repeated daily administration for 5 days. Comparative pharmacokinetics after IV and oral administration of 20 mg and 40 mg doses are summarized in Table 2.

Table 1

<table>
<thead>
<tr>
<th>Agent</th>
<th>Brand Name (Manufacturer)</th>
<th>Dosage Forms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esomeprazole</td>
<td>Nexium® (AstraZeneca, Wilmington, DE)</td>
<td>Delayed-release capsules: 20 mg, 40 mg</td>
</tr>
<tr>
<td></td>
<td>Nexium® IV (AstraZeneca)</td>
<td>Injection: 20-mg and 40-mg single-dose vial</td>
</tr>
<tr>
<td></td>
<td>Prevacid® (TAP Pharmaceuticals)</td>
<td>Delayed-release capsules: 15 mg, 30 mg</td>
</tr>
<tr>
<td></td>
<td>Prevacid® (TAP Pharmaceuticals)</td>
<td>Delayed-release oral suspension: 15-mg, 30-mg packets</td>
</tr>
<tr>
<td></td>
<td>Prevacid® IV (TAP Pharmaceuticals)</td>
<td>SoluTab delayed-release orally disintegrating tablets: 15 mg, 30 mg</td>
</tr>
<tr>
<td></td>
<td>Injection: 30-mg single-dose vial</td>
<td></td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>Protonix® (Wyeth Pharmaceuticals, Madison, NJ)</td>
<td>Delayed-release tablets: 20 mg, 40 mg</td>
</tr>
<tr>
<td></td>
<td>Protonix® IV (Wyeth)</td>
<td>Injection: 40-mg single-dose vial</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>Prilosec® OTC (Procter and Gamble, Cincinnati, OH)</td>
<td>Delayed-release tablets: 20 mg</td>
</tr>
<tr>
<td></td>
<td>Generics (Various)</td>
<td>Delayed-release capsules: 10 mg, 20 mg, 40 mg</td>
</tr>
<tr>
<td></td>
<td>Prilosec® (AstraZeneca)</td>
<td>Powder for oral suspension: 20 mg, 40 mg</td>
</tr>
<tr>
<td></td>
<td>Zegerid® (Santarus, San Diego, CA)</td>
<td>Delayed-release tablets: 20 mg</td>
</tr>
<tr>
<td>Rabeprazole</td>
<td>Aciphex® (Eisai, Teaneck, NJ)</td>
<td>Delayed-release tablets: 20 mg</td>
</tr>
</tbody>
</table>

Data from AstraZeneca, Wyeth Pharmaceuticals, TAP Pharmaceuticals, and Wolters Kluwer Health.

The bioavailability of oral esomeprazole is approximately 78% of that of IV esomeprazole.

The IV formulation improves the systemic bioavailability of PPIs because the acidity of the stomach and the upper duodenum and drug lability in this environment are avoided. Thus more drug is delivered to the site of action during the first few days of therapy.
1% of the dose is excreted unchanged in the urine. The same recommendations for dosage adjustments in special populations are suggested for IV esomeprazole as for oral esomeprazole. With oral esomeprazole, the area under the curve and peak concentration were increased slightly in the elderly; however, dosage adjustments based on age are not necessary. The pharmacokinetics of oral and IV esomeprazole have not been studied in patients younger than 18 years. The area under the curve and peak concentration of esomeprazole were slightly increased in women compared with men with both oral and IV administration; however, dosage adjustments based on gender are not necessary. Because less than 1% of the esomeprazole dose is eliminated unchanged in the urine, renal impairment is not expected to significantly affect the pharmacokinetics of esomeprazole.

The pharmacokinetics of oral esomeprazole was not altered in patients with mild to moderate hepatic impairment (Child-Pugh Classes A and B). In patients with severe hepatic insufficiency (Child-Pugh Class C), the area under the curve of esomeprazole was two- to threefold higher than in subjects with normal hepatic function. In patients with severe hepatic impairment (Child-Pugh Class C), a dose of 20 mg once daily should not be exceeded.

Lansoprazole

Peak plasma concentrations of lansoprazole occur after the completion of a 30-minute IV infusion. The mean (±SD) peak plasma concentrations after an IV infusion of lansoprazole 30 mg was 1705 ± 292 ng/mL. The mean area under the plasma concentration–time curve was 3192 ± 1745 ng/h/mL. The apparent volume of distribution of lansoprazole is approximately 15.7 L, with distribution primarily into the extracellular fluid. Lansoprazole is 97% plasma protein bound.

Lansoprazole is extensively metabolized in the liver, primarily to 2 metabolites with little to no antisecretory activity. After oral administration, no unchanged lansoprazole was excreted in the urine. The metabolites seem to be primarily eliminated in the bile.

The pharmacokinetics of 30 mg IV and oral lansoprazole doses are compared in Table 3.

Gender differences in lansoprazole pharmacokinetics have not been observed. Lansoprazole clearance is reduced, and the elimination half-life increased (50%–100%) in elderly subjects; however, dosage adjustments are not necessary because accumulation does not occur due to the short half-life (1.9–2.9 hours). The pharmacokinetics of IV lansoprazole have not been assessed in pediatric patients.

In patients with chronic hepatic disease, the mean plasma half-life of lansoprazole was prolonged from 1.5 hours to 3.2 to 7.2 hours after oral administration. An increase in mean area under the curve up to 500% was observed.

### Table 2

<table>
<thead>
<tr>
<th></th>
<th>20 mg Intravenous</th>
<th>20 mg Oral</th>
<th>40 mg Intravenous</th>
<th>40 mg Oral</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; day 1 (μmol/L)</td>
<td>3.32</td>
<td>0.78</td>
<td>6.77</td>
<td>2.97</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; day 5 (μmol/L)</td>
<td>3.86</td>
<td>1.57</td>
<td>7.51</td>
<td>4.6</td>
</tr>
<tr>
<td>AUC day 1 (μmol/h/L)</td>
<td>3.4</td>
<td>1.86</td>
<td>9.88</td>
<td>5.94</td>
</tr>
<tr>
<td>AUC day 5 (μmol/h/L)</td>
<td>5.11</td>
<td>3.92</td>
<td>16.21</td>
<td>12.55</td>
</tr>
<tr>
<td>T&lt;sub&gt;1/2&lt;/sub&gt; (h)</td>
<td>1.05</td>
<td>1.12</td>
<td>1.41</td>
<td>1.38</td>
</tr>
</tbody>
</table>

C<sub>max</sub>, peak concentration; AUC, area under the plasma concentration–time curve; T<sub>1/2</sub>, half-life. Data from Wilder-Smith CH et al.16

### Table 3

<table>
<thead>
<tr>
<th></th>
<th>Intravenous (n = 64)</th>
<th>Oral (n = 62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability (%)</td>
<td>&gt; 80</td>
<td></td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; (h)</td>
<td>0.5†</td>
<td>1.5–1.8</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)*</td>
<td>1652–1884</td>
<td>807–1052</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;24h&lt;/sub&gt; (ng/h/mL)</td>
<td>3192–3611</td>
<td>2422–3101</td>
</tr>
<tr>
<td>T&lt;sub&gt;1/2&lt;/sub&gt; (h)</td>
<td>1.13–1.3</td>
<td>1.1–1.24</td>
</tr>
</tbody>
</table>

T<sub>max</sub>, time to peak concentration; C<sub>max</sub>, peak concentration; AUC, area under the plasma concentration–time curve; T<sub>1/2</sub>, half-life. Data from Freston FW et al;19,20 and TAP Pharmaceuticals.18

*Range of means from 2 studies and multiple time points.
†At completion of the 30-minute infusion.
observed at steady-state in patients with hepatic impairment. Dosage reductions should be considered in patients with severe hepatic disease.\textsuperscript{18}

In patients with severe renal insufficiency, lansoprazole protein binding, half-life, and total area under the curve are reduced, whereas peak concentration and time to peak concentration are unchanged. No adjustments in dose are necessary because of these changes.\textsuperscript{18}

Pantoprazole

IV pantoprazole is given as a 15-minute infusion. The serum concentration time curve increases proportionally to the IV doses from 10 mg to 80 mg. Peak serum concentrations occur at the end of the IV infusion and are 5.52 μg/mL after a 40-mg dose.\textsuperscript{15} After a single 40-mg IV dose administered over 15 minutes, plasma concentrations at the end of the infusion ranged from 3.21 μg/mL to 7.05 μg/mL in 12 healthy subjects. The mean half-life was 1.9 hours.\textsuperscript{21}

The total clearance of pantoprazole is 7.6 L/h to 14 L/h, and its apparent volume of distribution is 11 L to 23.6 L. Serum protein binding is 98%, primarily to albumin.

Pantoprazole is extensively metabolized in the liver through the CYP system after both oral and IV administration.\textsuperscript{12,15} Lansoprazole, omeprazole, pantoprazole, and rabeprazole are metabolized by the CYP2C19 enzyme system. In subjects with CYP2C19 deficiency (eg, 3% of Caucasians and African Americans and 17%–23% of Asians) due to genetic polymorphism (slow metabolizers), the elimination half-life of pantoprazole is increased to 3.5 to 10 hours. Accumulation remains minimal (≤ 23%) with once-daily dosing in this population.\textsuperscript{12,15} Pantoprazole also undergoes metabolism to a minor extent by CYPs 3A4, 2D6, and 2C9.\textsuperscript{12} Approximately 71% of the dose is excreted in the urine as metabolites, with another 18% of the dose excreted in the feces through biliary excretion. No unchanged drug is excreted in the urine.\textsuperscript{12,15}

Liver dysfunction can decrease the clearance of pantoprazole to an extent similar to that observed in slow metabolizers. In patients with severe cirrhosis, the elimination half-life is increased to 7 to 9 hours.\textsuperscript{12,15} Dosage adjustments are not necessary in patients with mild to moderate hepatic dysfunction.\textsuperscript{12,15} In patients with severe hepatic dysfunction, the potential for drug accumulation (≤ 21%) with once-daily dosing must be weighed against the potential for reduced acid control with administration every other day.\textsuperscript{12,15}

Severe renal impairment and hemodialysis have no impact on the clearance of pantoprazole.\textsuperscript{12,15} Dosage adjustments are not needed in patients with renal dysfunction or in the elderly.\textsuperscript{12,15}

**Pharmacodynamics: Influence on Intragastric pH**

Mean intragastric pH over a 24-hour period was determined after 5 days of once daily esomeprazole 20 mg or 40 mg. The dose was infused intravenously over 30 minutes. The percentage of time the gastric pH was greater than 4 on day 5 was 49.5% (95% confidence interval, [CI] 41.9%–57.2%) with esomeprazole 20 mg and 66.2% (95% CI, 62.4%–70.0%) with esomeprazole 40 mg.\textsuperscript{14}

Mean intragastric pH over a 24-hour period was comparable after administration of oral and IV lansoprazole 30 mg in a crossover study. Compared with oral lansoprazole, IV lansoprazole produced a greater intragastric pH within the first hour of administration, both on the first day of administration and on day 5.\textsuperscript{19,22} Oral and IV lansoprazole 30-mg doses produced comparable reductions in basal and maximal acid output in another study, although IV administration was associated with a greater first-dose effect and less first-dose variability.\textsuperscript{19,23} With once-daily oral administration, the intragastric pH was lower during the second 12 hours of the dosing interval, and intragastric pH was increased for a greater period of time with twice-daily IV lansoprazole.\textsuperscript{24–26} Comparable intragastric pH changes were observed when lansoprazole 30 mg was administered intravenously over 2 minutes or over 2 hours.\textsuperscript{25}

**Intravenous PPIs**

Compared with oral lansoprazole, IV lansoprazole produced a greater intragastric pH within the first hour of administration.
greater than 3 in 99%, pH greater than 4 in 99%, pH greater than 5 in 94%, and pH greater than 6 in 84% in healthy volunteers.28

Thirty-three healthy patients were given nasogastric lansoprazole or IV pantoprazole to determine the impact of these agents on 24-hour intragastric pH. Patients were given 5 days of lansoprazole 30 mg or pantoprazole 40 mg once daily, then were switched to the other agent for another 5 days. pH evaluations were done on days 1 and 5 of each therapy. The mean 24-hour pH was 3.05 on day 1 with lansoprazole and 2.76 with pantoprazole. These values changed to 3.65 and 3.45 after 5 days of therapy.29

**Indications**

The US Food and Drug Administration (FDA)-approved indications are different for the IV PPIs; however, they all are probably effective in the treatment of these medical conditions. Table 4 compares the FDA-approved indications for the available injectable PPIs.

**Clinical Efficacy**

**Esomeprazole**

The IV esomeprazole prescribing information contains information on 4 multicenter, open-label, crossover studies comparing IV and oral esomeprazole in patients with symptoms of gastroesophageal reflux disease (GERD), with or without erosive esophagitis. A total of 206 patients (aged 18–72 years; 112 female; 110 Caucasian, 50 African American, 10 Asian, and 36 other race) were randomized to receive IV or oral esomeprazole 20 mg or 40 mg once daily for 10 days, and then were switched to the alternate route of therapy for 10 days at the same dose. The IV formulation was administered as a 3-minute injection in 2 studies and as a 15-minute infusion in the other 2 studies. The IV and oral formulations produced similar suppression of basal acid output and maximal acid output. Symptomatic improvement was not assessed.14

The combined results of 2 studies comparing the effects of oral and IV esomeprazole on intragastric pH have been reported. In an open-label, randomized, crossover study conducted in Switzerland, the effects of oral esomeprazole 20 mg and IV esomeprazole 20 mg were compared in 24 healthy subjects. In the other, double-dummy, randomized, crossover study conducted in Sweden, the effects of oral esomeprazole 40 mg and IV esomeprazole 40 mg were compared in 40 healthy subjects. Subjects received esomeprazole as a 30-minute infusion once daily for 5 days or orally once daily for 5 days, followed by a 13-day washout period, and then administration of the alternate agent for 5 days. Continuous 24-hour intragastric pH monitoring was conducted at baseline and on days 1 and 5 of drug administration. In both studies, acid suppression and pharmacokinetics were compared after day 1 and day 5 of daily dosing. On day 1, the time spent with an intragastric pH greater than 4 was slightly greater with the 40-mg IV dose (10.1 hours) compared with the 40-mg oral dose (8.8 hours, difference 1.3 hours; 95% CI, 0.3–2.4 hours). No differences were observed in the amount of time spent with intragastric pH greater than 4 between the oral and IV routes on either days at the 20-mg dose and on day 5 with the 40-mg dose. At the 20-mg dose, the amount of time with intragastric pH greater than 4 was 7.3 hours with IV administration and 6.6 hours with oral administration on day 1, and 11.9 hours with IV administration and 12.3 hours with oral administration on day 5. At the 40-mg dose, the amount of time with intragastric pH greater than 4 was 15.9 hours with IV administration and

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**Table 4**

<table>
<thead>
<tr>
<th>FDA-Approved Indications for the Injectable Proton Pump Inhibitors</th>
<th>Esomeprazole</th>
<th>Lansoprazole</th>
<th>Pantoprazole</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short-term treatment (up to 7 d)</strong> of all grades of erosive esophagitis in patients unable to take oral therapy</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Short-term treatment (up to 10 d)</strong> of gastroesophageal reflux disease associated with a history of erosive esophagitis in patients for whom oral therapy is not possible or appropriate</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Treatment of pathologic hypersecretory conditions associated with Zollinger-Ellison syndrome or other neoplastic conditions</td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

FDA, US Food and Drug Administration. Data from AstraZeneca,14 Wyeth Pharmaceuticals,15 and TAP Pharmaceuticals.18

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Intravenous PPIs continued
Intravenous PPIs

15.3 hours with oral administration on day 5.16

Oral and IV esomeprazole 40 mg have also been compared in a randomized, double-blind study including 246 patients with erosive esophagitis at 10 sites in South Africa. During the first week of therapy, patients received esomeprazole 40 mg once daily orally or as a 3-minute IV injection or 30-minute IV infusion. All patients then received oral esomeprazole 40 mg once daily for 3 weeks, with healing assessed at week 4. Healing rates were comparable regardless of the route of administration during the first week: 79.7% (95% CI, 69.2%-88%) for the 3-minute injection group, 80.2% (95% CI, 69.9%-88.3%) for the 30-minute infusion group, and 82.6% (95% CI, 72.9%-89.9%) for the oral group.30,31

Acid control with IV esomeprazole and IV pantoprazole has been compared in an open-label, randomized, crossover study in 25 healthy volunteers. Subjects received esomeprazole 40 mg or pantoprazole 40 mg as a 15-minute infusion once daily for 5 days, followed by a 13-day washout period, and then administration of the alternate agent for 5 days. Continuous 24-hour intragastric pH monitoring was conducted at baseline and on days 1 and 5 of drug administration. At baseline, the mean amount of time over 24 hours that the intragastric pH was greater than 4 was 2.6 hours (95% CI, 1.3-4 hours), and the median pH was 1.6. Time with intragastric pH greater than 4 was greater after esomeprazole than after pantoprazole during the first day and fifth day of administration. The difference was apparent within the first 4 hours of administration of the first dose. Esomeprazole was associated with 8.3 hours and 13.9 hours with an intragastric pH greater than 4 on days 1 and 5, compared with 5.3 hours and 9 hours for pantoprazole on days 1 and 5 (Figure 1; day 1 P < .001, day 5 P < .0001). During the first 4 hours of dosing on day 1, an intragastric pH greater than 4 was achieved for esomeprazole (P < .001) over the first 24 hours and was 4.3 with esomeprazole and 3.2 with pantoprazole (P < .0001) on day 5. Overall, esomeprazole was associated with faster and greater intragastric acid control than pantoprazole at the 40-mg dose.32

Lansoprazole

A multicenter, double-blind, placebo-controlled study enrolled 87 patients with erosive esophagitis. These patients were treated with oral lansoprazole 30 mg once daily for 7 days and then switched to IV lansoprazole 30 mg or IV placebo (normal saline) once daily for 7 days. Maximum and basal acid output were assessed 21 hours after the last oral and IV dose. The oral and IV formulations produced comparable suppression of maximum and basal acid output. The results of this efficacy study are summarized in Table 5.18

Overall, esomeprazole was associated with faster and greater intragastric acid control than pantoprazole at the 40-mg dose.

1.7 hours with esomeprazole, compared with 0.6 hours with pantoprazole (P < .0001). Median pH was 3.1 with esomeprazole and 2.3 with pantoprazole (P < .01) over the first 24 hours and was 4.3 with esomeprazole and 3.2 with pantoprazole (P < .0001) on day 5. Overall, esomeprazole was associated with faster and greater intragastric acid control than pantoprazole at the 40-mg dose.32

The effect of IV lansoprazole on gastric acid secretion in patients with postoperative stress was assessed in an open-label study enrolling 82

![Figure 1. Time with intragastric pH > 4. Reprinted with permission from Wilder-Smith CH et al.32](image-url)

Table 5

| Acid Output in Patients with Erosive Esophagitis After 7 Days of Lansoprazole or Placebo Therapy |
|---------------------------------|-----------------|-----------------|-----------------|
|                                 | Oral Lansoprazole | Intravenous Lansoprazole | Intravenous Placebo |
| Median maximum acid output      | 7.16 (n = 80)    | 7.64 (n = 56)    | 26.90* (n = 17) |
| Median basal acid output        | 0.77 (n = 81)    | 0.51 (n = 55)    | 3.19* (n = 16) |

Data from TAP Pharmaceuticals.18

*P < .001, intravenous lansoprazole vs placebo.

†P = .005, intravenous lansoprazole vs placebo.
hospitalized patients ages 20 to 75 years. Patients received lansoprazole 15 mg twice daily (n = 41) or lansoprazole 30 mg twice daily (n = 41) for 3 days after surgery under general anesthesia for gastrointestinal disease. Intragastric pH was assessed every 8 hours. For patients with pretreatment intragastric pH less than 3, responses were defined as excellent, good, fair, or poor. For patients with pretreatment intragastric pH above 3, responses were defined as excellent, good, fair, or poor. Efficacy was excellent in 20 (52.6%) of 38 assessable patients treated with lansoprazole 15 mg and 22 (59.5%) of 37 assessable patients treated with lansoprazole 30 mg. An additional 5 patients in the 15-mg group and 6 in the 30-mg group achieved a good response, for an overall assessment of excellent or good in 65.8% in the 15-mg group and 75.7% in the 30-mg group.

IV lansoprazole has been assessed in an open-label pilot study enrolling 47 patients with upper gastrointestinal bleeding due to gastric or duodenal ulcers. Patients received IV lansoprazole 15 mg twice daily (n = 26) or 30 mg twice daily (n = 20) for 7 days. The hemostatic effects, determined by gastric probe or endoscope, were rated excellent (if bleeding was stopped within 36 hours), good (if bleeding was stopped within 72 hours), fair (if bleeding was stopped within 7 days), or poor (if bleeding was not stopped within 7 days or treatment was changed). Hemostasis was rated excellent in 14 (63.6%) of 22 patients treated with lansoprazole 15 mg and 13 (72.2%) of 18 patients treated with lansoprazole 30 mg. An additional 4 patients in the 15-mg group and 3 patients in the 30-mg group achieved a response rated good, for an overall assessment of excellent or good in 81.8% in the 15-mg group and 88.9% in the 30-mg group.

Pantoprazole
Oral and IV pantoprazole are equally effective in suppressing gastric acid output and providing symptomatic control in patients with GERD. Pantoprazole is also effective in decreasing antacid use and decreasing acid output in patients with symptomatic esophagitis and GERD.

Efficacy of pantoprazole in controlling GERD symptoms was assessed in an observational study conducted in hospitalized patients in 17 hospitals in Germany. Pantoprazole was administered to 269 patients (63.6%) of 22 patients treated with lansoprazole 15 mg and 13 (72.2%) of 18 patients treated with lansoprazole 30 mg. An additional 4 patients in the 15-mg group and 3 patients in the 30-mg group achieved a response rated good, for an overall assessment of excellent or good in 81.8% in the 15-mg group and 88.9% in the 30-mg group.

In a similar open-label study, pantoprazole was administered intravenously for 5 to 7 days, followed by oral administration for up to 7 weeks in 176 patients with reflux esophagitis (stage II or III, Savary-Miller classification). The safety and efficacy of pantoprazole therapy was assessed in 142 patients who completed the study. Healing was achieved in 114 of 142 patients (80%) at week 4 and 132 of 142 patients (93%) at week 8. After 2 weeks, heartburn, acid regurgitation, and pain on swallowing resolved in 87%, 90%, and 93% of patients, respectively. The reflux symptom score was improved within 4 days of initiating IV pantoprazole.

IV pantoprazole has also been assessed in an observational study conducted in hospitalized patients in 17 hospitals in Germany. Pantoprazole was administered to 269 patients and 57.1% of patients switched to placebo.

Pantoprazole 40 mg once daily administered intravenously for 5 to 7 days, followed by oral administration for up to 8 weeks, has been assessed in 110 patients with moderate or severe GERD (stage II or III, Savary-Miller classification). Complete healing in the intention-to-treat group occurred in 85 of 110 patients (77%) at 4 weeks and 93 of 110 patients (85%) at 8 weeks. After 2 weeks, heartburn, acid regurgitation, and pain on swallowing resolved in 97%, 98%, and 100% of patients, respectively, with these symptoms at baseline. Marked improvement in key symptoms was reported after the third day of IV pantoprazole therapy.

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IV pantoprazole has also been assessed in an observational study conducted in hospitalized patients in 17 hospitals in Germany. Pantoprazole was administered to 269 patients and 57.1% of patients switched to placebo.

Pantoprazole 40 mg once daily administered intravenously for 5 to 7 days, followed by oral administration for up to 8 weeks, has been assessed in 110 patients with moderate or severe GERD (stage II or III, Savary-Miller classification). Complete healing in the intention-to-treat group occurred in 85 of 110 patients (77%) at 4 weeks and 93 of 110 patients (85%) at 8 weeks. After 2 weeks, heartburn, acid regurgitation, and pain on swallowing resolved in 97%, 98%, and 100% of patients, respectively, with these symptoms at baseline. Marked improvement in key symptoms was reported after the third day of IV pantoprazole therapy.
solution in 99% of cases. It was administered peripherally in 82% of patients and centrally in 18%. The 40-mg dose was administered to 94.7% of patients, whereas 5% received 20 mg, and 0.3% received 80 mg. The mean duration of IV pantoprazole therapy was 6 days; 90% of patients received IV pantoprazole for no more than 10 days. An orally administered acid inhibitor was continued in 84% of patients during their hospitalization and in 72% of patients after discharge. Concomitant illness was present in 214 patients (80%), primarily circulatory (23%), digestive (17%), or endocrine, nutritional, or metabolic (17%). Improvement was observed in 241 patients (90%). At assessment after the last pantoprazole infusion, complete healing was reported for 7.3% of patients, significant improvement was reported for 70.2% of patients, and slight improvement was reported for 14.5% of patients. Physicians judged the efficacy of the IV pantoprazole therapy as “very good” or “good” in 89% of patients. Tolerability was assessed to be “very good” or “good” in 98% of patients.41

IV pantoprazole has been compared with IV ranitidine in the prevention of peptic ulcer rebleeding in 133 patients.42 The initial bleeding was controlled with endoscopic homeostasis. Patients were then randomized to treatment with pantoprazole or ranitidine, and the study medication was given within 1 hour of the endoscopic homeostasis. The pantoprazole was given as a 40-mg IV dose and then followed by an 8-mg/h continuous infusion for 2 days. The ranitidine was given as a 50-mg IV dose and then followed by a 12.5-mg/h continuous infusion for 2 days. Endoscopic examination was repeated 48 hours after the initial endoscopic procedure or on suspicion of rebleeding. Follow-up on the patient’s status was continued for 8 more days, for a total of 10 days of observation. The study was completed per protocol by 61 patients in the pantoprazole group and 58 patients in the ranitidine group. The rate of rebleed after 48 hours of therapy was 10% in both groups, and the mortality rate after 10 days was 1.5% in both groups.42

The efficacy of pantoprazole IV after oral PPI therapy has been assessed in 14 patients with Zollinger-Ellison syndrome.43 Before the switch to IV pantoprazole, 9 patients were taking oral omeprazole (3, 20 mg once daily; 3, 20 mg twice daily; and 1 each, 40, 60, or 100 mg twice daily), and 5 patients were taking oral lansoprazole (2 each, 30 mg once daily or twice daily; and 1, 60 mg twice daily). Acid secretion was controlled in all patients taking oral PPI therapy, with a mean acid output of 0.55 mEq/h. Patients were then switched to IV pantoprazole 80 mg twice daily for 7 days, with the dose titrated upward to a maximum of 240 mg/24 hours if acid output was not controlled. Acid output (AO) was controlled (AO < 5 mEq/h or < 5 mEq/h after gastric acid-reducing surgery) in 13 of 14 patients (93%) at the 80-mg dose administered twice daily. One patient previously treated with oral omeprazole 100 mg twice daily did not respond to pantoprazole therapy at 80 mg or 120 mg twice daily (AO = 12.7 mEq/h on day 7, from a baseline AO of 0.65 mEq/h with oral omeprazole).43

Contraindications
Use of any of the injectable PPIs is contraindicated in patients with known hypersensitivity to the drug and any of the formulation ingredients (see Table 6).

Warnings and Precautions
Treatment with any of these IV formulations should be continued as soon as the patient is able to resume treatment with an oral PPI.14,15,18 Symptomatic response to therapy with any PPI does not preclude the presence of gastric malignancy.14,15,18 The safety and effectiveness of any of these PPIs has not been established in pediatric patients.14,15,18

Esomeprazole
Esomeprazole is classified as Pregnancy Category B. Esomeprazole should be used during pregnancy only if clearly needed.14 Esomeprazole excretion in milk has not been assessed; however, omeprazole concentrations have been reported to be negligible in breast milk (levels that are well below the amount expected to cause adverse effects in nursing infants).12,14 The safety and effectiveness of any of these PPIs has not been established in children.14,15,18

Table 6
Chemical Classification and Product Ingredients of the Intravenous Proton Pump Inhibitors

<table>
<thead>
<tr>
<th>Chemical classification</th>
<th>Esomeprazole</th>
<th>Lansoprazole</th>
<th>Pantoprazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzimidazole</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Edetate disodium</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Mannitol</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Meglumine</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Sodium hydroxide</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

Data from AstraZeneca,14 Wyeth Pharmaceuticals,15 and TAP Pharmaceuticals.18
been measured in breast milk after omeprazole therapy. Discontinuation of nursing or esomeprazole is recommended in breast-feeding mothers due to the potential risks of adverse effects.14

Lansoprazole
Lansoprazole is classified in Pregnancy Category B. Lansoprazole should be used during pregnancy only if clearly needed.18

Lansoprazole or its metabolites are excreted in the milk of rats. It is not known whether lansoprazole is excreted in human milk. Owing to the potential for adverse effects in the infant, use in nursing mothers is not recommended.18

Pantoprazole
Pantoprazole is classified in Pregnancy Category B. Controlled studies in pregnant women are lacking.15

Pantoprazole and its metabolites are excreted in the milk of rats. It is unknown whether pantoprazole is excreted in human milk, but the manufacturer recommends that either nursing or the drug be discontinued.15

No changes in cortisol, testosterone, triiodothyronine, thyroxine, thyroid-stimulating hormone, thyronine-binding protein, parathyroid hormone, insulin, glucagon, renin, aldosterone, follicle-stimulating hormone, luteinizing hormone, prolactin and growth hormone have been reported.15

Adverse Reactions
All 3 of these PPIs are well tolerated.14 Common adverse events included headache, flatulence, nausea, dyspepsia, and abdominal pain. A complete list of the adverse events reported with pantoprazole can be found in the oral and IV product labeling.

Reactions specific to the IV route have included mild itching at the injection site and mild focal erythema at the IV insertion site. The incidence and nature of adverse events did not seem to differ between oral and IV administration.

Drug Interactions
Changes in pH might influence the absorption of some drugs from the stomach. PPIs might decrease the absorption of ketoconazole, ampicillin esters, and iron salts and increase the absorption of benzyl penicillin by raising the pH of the stomach.14,15,18

Esomeprazole
Esomeprazole is extensively metabolized in the liver by CYP2C19 and CYP3A4.14

Esomeprazole is not likely to inhibit CYPs 1A2, 2A6, 2C9, 2D6, 2E1, or 3A4. Drug interactions are not anticipated with substrates of these enzymes. Drug interaction studies have shown that esomeprazole does not have any clinically important interactions with phenytoin, warfarin, quinidine, clarithromycin, or amoxicillin. However, postmarketing reports have described increases in international normalized ratio (INR) and prothrombin time in patients receiving concomitant esomeprazole and warfarin. Monitoring is recommended in patients receiving this combination.14

Esomeprazole might interfere with CYP2C19. Administration of esomeprazole 30 mg with diazepam, a CYP2C19 substrate, resulted in a 45% reduction in diazepam clearance and increased diazepam plasma levels. This drug interaction is not believed to be clinically important.14

The pharmacokinetics of esomeprazole were not altered by concomitant administration of diazepam, phenytoin, oral contraceptives, or quinidine.14 Concomitant administration with naproxen or rofecoxib did not result in changes in the pharmacokinetics of esomeprazole or either of the nonsteroidal anti-inflammatory drugs.14

Lansoprazole
Lansoprazole is a CYP3A and CYP2C19 substrate. Interactions have not been observed between lansoprazole and warfarin, diazepam, phenytoin, propranolol, antipyrine, indomethacin, ibuprofen, prednisone, or clarithromycin in healthy subjects. Administration of lansoprazole with theophylline resulted in a small (10%) increase in theophylline clearance. The dose of theophylline might need to be adjusted when lansoprazole therapy is initiated or discontinued.18

Although neither a pharmacokinetic nor pharmacodynamic interaction was observed between lansoprazole and warfarin in healthy subjects, cases of increased INR and prothrombin time have been reported in patients receiving PPIs, including lansoprazole and warfarin concomitantly. INR or prothrombin time monitoring is recommended in patients receiving lansoprazole and warfarin concomitantly.18

Pantoprazole
Pantoprazole does not seem to affect the metabolism of other medications. Nor is the metabolism of pantoprazole affected by other medications.15

Dosing
Esomeprazole
The recommended dose of injectable esomeprazole is 20 mg or 40 mg once
daily by IV injection (no less than 3 minutes) or IV infusion (10 to 30 minutes). Esomeprazole should not be administered concomitantly with any other medications through the same line or tubing. The line should always be flushed with either 0.9% Sodium Chloride Injection USP, Lactated Ringer’s Injection USP, or 5% Dextrose Injection USP before and after administration of the esomeprazole.14

A dose of 20 mg should not be exceeded in patients with severe hepatic impairment (Child-Pugh Class C). No dosage adjustments are necessary in the elderly, patients with renal dysfunction, or on the basis of gender.14

Lansoprazole
The recommended dose is 30 mg once daily for up to 7 days, administered intravenously over 30 minutes in 50 mL of 0.9% Sodium Chloride Injection USP, Lactated Ringer’s Injection USP, or 5% Dextrose Injection USP. Use of an in-line filter is required. A dedicated line is not required; however, the line should be flushed before and after administration of lansoprazole. Lansoprazole injection should not be administered with other drugs or diluents.18

Lansoprazole for injection must be reconstituted with 5 mL of Sterile Water for Injection USP, producing a solution containing lansoprazole 6 mg/mL (30 mg/5 mL). Use of other diluents might result in precipitation or the formation of particulates.18 The reconstituted solution should be further diluted in 50 mL of 0.9% Sodium Chloride Injection USP, Lactated Ringer’s Injection USP, or 5% Dextrose Injection USP. Lansoprazole solution should be administered intravenously with the supplied in-line filter. The filter must be used to remove precipitate that might form when the reconstituted drug is mixed with IV solutions.18

Pantoprazole
The recommended adult dose of IV pantoprazole is 40 mg given once daily by IV infusion for 7 to 10 days.15

The rate of the infusion should be 7 mL/min and last approximately 15 minutes.15 The pantoprazole solution should be given through a dedicated IV line or through a Y-site.15 The infusion line should be flushed before and after pantoprazole administration with either 5% Dextrose Injection USP, 0.9% Sodium Chloride Injection USP, or Lactated Ringer’s Injection USP.15 Pantoprazole is incompatible with magnesium and might be incompatible with products containing zinc.15

Dosage adjustments are not necessary in the elderly, patients with renal insufficiency, and patients with mild or moderate hepatic impairment. In patients with severe hepatic impairment, the potential for drug accumulation (>21%) with once-daily dosing must be weighed against the potential for reduced acid control with administration every other day.15

The safety and effectiveness of pantoprazole in pediatric patients have not been established.15

Table 7 summarizes the IV dose and administration for esomeprazole, lansoprazole, and pantoprazole. It should be noted that many clinicians use IV PPIs for the treatment of ulcer bleeding. Although the only published clinical studies have reported on the use of omeprazole with an 80-mg bolus followed by an 8 mg/h continuous infusion for this clinical indication, many have extrapolated this to pantoprazole, lansoprazole, and esomeprazole, using an 80-mg, 60-mg, and 40-mg bolus, respectively, followed by an 8-mg/h, 6-mg/h, and 4-mg/h infusion of these agents. The effectiveness of these doses are as yet unknown but again have become widely used for this indication.

Product Availability
Esomeprazole
Esomeprazole is available as a sterile, freeze-dried, porous cake or powder, in a 5-mL vial.14 It is intended for IV administration after reconstitution with 0.9% Sodium Chloride Injection USP, Lactated Ringer’s Injection USP, or 5% Dextrose Injection USP. Available vials contain esomeprazole sodium 21.3 mg or 42.5 mg, equivalent to esomeprazole 20 mg or 40 mg, edetate disodium 1.5 mg, and sodium hydroxide as needed for pH adjustment. The stability of the reconstituted solution is pH dependent, with the rate of degradation increasing with decreasing pH.14

Lansoprazole
Lansoprazole is available as a lyophilized powder in vials containing lansoprazole 30 mg, mannitol 60 mg, meglumine 10 mg, and sodium hydroxide 3.45 mg. Each pack contains one 30-mg single-dose vial and one in-line filter (1.2-μm pore size).18

Upon reconstitution with sterile water for injection, the solution has a pH of 11. The pH is approximately 10.2 after further dilution with 0.9% Sodium Chloride for Injection USP, 10 after further dilution with Lactated Ringer’s Injection USP, and 9.5 after dilution with 5% Dextrose Injection USP. The rate of degradation of the compound in aqueous solution increases with decreasing pH.18 The reconstituted solution can be held for 1 hour when stored at 25°C (77°F) before further dilution.18

Pantoprazole
The IV formulation of pantoprazole is supplied as a freeze-dried powder in a clear glass vial fitted with a rubber stopper. Each vial contains pantoprazole sodium (equivalent to pantoprazole 40 mg).15

The dry powder in the pantoprazole vial should be reconstituted with 10 mL
of 0.9% Sodium Chloride Injection, USP. Before administration this solution should be diluted with 100 mL of 5% Dextrose Injection USP, 0.9% Sodium Chloride Injection USP, or Lactated Ringer’s Injection USP. The final concentration of the diluted solution is approximately 0.4 mg/mL.\textsuperscript{15}

The reconstituted solution can be stored at room temperature but needs to be used within 24 hours.\textsuperscript{15}

The available dosage forms for esomeprazole, lansoprazole and pantoprazole are summarized in Table 8.

### Conclusion

IV administration of the PPI is a faster way to achieve gastric acid suppression than oral administration of the same agent. Peak suppression after IV administration occurs within hours, compared with several days later after oral administration. Thus the IV route of administration offers a faster onset of gastric suppression, achievement of intragastric pH closer to neutrality, and better bioavailability. All of the IV formulations are approved for different indications; the key differences between them relate to their ability to reach specific gastric pH, time to

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**Table 7**  
Intravenous Dose and Administration of Intravenous Proton Pump Inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Esomeprazole</th>
<th>Lansoprazole</th>
<th>Pantoprazole</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose</strong></td>
<td>GERD/erosive esophagitis: 20 mg or 40 mg qd for up to 10 d</td>
<td>Erosive esophagitis: 30 mg qd for up to 7 d</td>
<td>GERD/erosive esophagitis: 40 mg qd for 7–10 d Hypersecretory conditions: 80 mg every 12 h</td>
</tr>
<tr>
<td><strong>Administration</strong></td>
<td>3-min injection or 10- to 30-min infusion</td>
<td>30-min infusion</td>
<td>2-min injection or 15-min infusion</td>
</tr>
<tr>
<td><strong>In-line filter required?</strong></td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
| **Reconstitution** | • 5 mL 0.9% Sodium Chloride Injection USP for 3-min injection  
• 5 mL 0.9% Sodium Chloride Injection USP, Lactated Ringer’s Injection USP, or 5% Dextrose Injection USP if undergoing further dilution for infusion | 5 mL sterile water for Injection USP             | 10 mL 0.9% Sodium Chloride Injection USP        |
| **Dilution for infusion** | Dilute to 50 mL with 0.9% Sodium Chloride Injection USP, Lactated Ringer’s Injection USP, or 5% Dextrose Injection USP for the 10- to 30-min infusion. Administer within 12 h when diluted with 0.9% Sodium Chloride or Lactated Ringer’s and within 6 h when diluted with 5% Dextrose | Dilute in 50 mL 0.9% Sodium Chloride Injection USP, Lactated Ringer’s Injection USP, or 5% Dextrose Injection USP for 30-min infusion. Administer within 24 h when diluted with 0.9% Sodium Chloride or Lactated Ringer’s and within 12 h when diluted with 5% Dextrose | Dilute to 100 mL with 5% Dextrose Injection USP, 0.9% Sodium Chloride Injection USP, or Lactated Ringer’s Injection USP for 15-min infusion. The diluted solution should be administered within 24 h |

GERD, gastroesophageal reflux disease.
Data from AstraZeneca,\textsuperscript{14} Wyeth Pharmaceuticals,\textsuperscript{15} and TAP Pharmaceuticals.\textsuperscript{18}
maintain a specific gastric pH, and ease of use of the IV formulation (eg, reconstitution, requirement of in-line filters, infusion times).

Main Points

- Intravenous (IV) formulations of proton pump inhibitors (PPIs) improve the systemic bioavailability of PPI because the acidity of the stomach and the upper duodenum and drug lability in this environment are avoided; thus, more drug is delivered to the site of action during the first few days of therapy.

- The US Food and Drug Administration–approved indications are different for the IV PPIs; however, they all are probably effective in the treatment of these medical conditions.

- Use of any of the injectable PPIs is contraindicated in patients with known hypersensitivity to the drug and any of the formulation ingredients.

- Treatment with the IV formulations of esomeprazole, lansoprazole, and pantoprazole should be discontinued as soon as the patient is able to resume treatment with an oral PPI; symptomatic response to therapy with any PPI does not preclude the presence of gastric malignancy; the safety and effectiveness of any of these PPIs has not been established in pediatric patients.

- All 3 of these PPIs are well tolerated: common adverse events included headache, flatulence, nausea, dyspepsia, and abdominal pain; reactions specific to the IV route have included mild itching at the injection site and mild focal erythema at the IV insertion site.

- Changes in pH might influence the absorption of some drugs from the stomach; PPIs might decrease the absorption of ketoconazole, ampicillin esters, and iron salts and increase the absorption of benzyl penicillin by raising the pH of the stomach.

References


Intravenous PPIs continued


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