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Intravenous Lansoprazole

In Erosive Oesophagitis

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Contents

Abstract

▲ An intravenous formulation of lansoprazole, a proton pump inhibitor, is approved for use in patients with erosive oesophagitis who are temporarily unable to take oral lansoprazole.

▲ In healthy volunteers, oral and intravenous lansoprazole 30 mg/day were equivalent in suppressing basal and pentagastrin-stimulated maximum gastric acid output. Moreover, the mean 24-hour intragastric pH did not differ significantly following oral or intravenous administration of lansoprazole and was significantly higher with both formulations than with intravenous polyethylene glycol vehicle.

▲ After treatment for 7 days in patients with erosive oesophagitis, intravenous lansoprazole (30 mg/day) recipients had significantly lower median stimulated and basal gastric acid output measurements than placebo recipients. Median pentagastrin-stimulated gastric acid output levels were equivalent after 7 days treatment with intravenous or oral lansoprazole.

▲ Intravenous lansoprazole is generally well tolerated. All adverse events experienced by patients with erosive oesophagitis who received intravenous lansoprazole were mild or moderate in severity.

Features and properties of intravenous lansoprazole (Prevacid®)	
Indication	
Short-term use in patients with erosive oesophagitis who are temporarily unable to take oral lansoprazole	
Mechanism of action	
Proton pump inhibitor	Inhibits acid secretion via selective inhibition of H^+/K^+-adenosine triphosphatase in parietal cells
Dosage and administration	
Approved dosage	30mg infused over 30 minutes
Frequency of administration	Once daily
Pharmacokinetic properties of lansoprazole (30 mg/day) after intravenous administration for 7 days in healthy volunteers	
Peak plasma concentration (C_{max})	1652 ng/mL
Time to C_{max}	0.5h
Area under the concentration-time curve from 0–24 hours	3365 ng • h/mL
Elimination half-life	1.17h
Adverse events	
Most frequent (≥1%)	Nausea, headache, injection-site pain and reactions

Lansoprazole is a proton pump inhibitor which, as an oral formulation, is used extensively in the management of acid-related disorders, including erosive oesophagitis (reviewed in *Drugs*).[1] There are occasions when patients cannot take medications orally, or it is more convenient for them to be treated intravenously.[2] For this reason, an intravenous formulation of lansoprazole (Prevacid® IV)[1] has been developed for use in patients with erosive oesophagitis.

1. Pharmacodynamic Properties

The pharmacological properties of oral lansoprazole are well established.[1] This section focuses on the pharmacodynamic properties of intravenous lansoprazole as reported in two open-label trials in healthy volunteers (reported as study 1 and study 2 in a fully published paper[3]). In both studies, oral or intravenous lansoprazole 30mg was administered once daily. In study 1, 29 volunteers received oral lansoprazole for 7 days, and then intravenous lansoprazole in 0.9% sodium chloride for 7 days. In study 2, 36 volunteers received intravenous lansoprazole in polyethylene glycol (PEG), intravenous lansoprazole in 0.9% sodium chloride, oral lansoprazole or intravenous PEG vehicle for 5 days each. For the intravenous formulations, only data pertaining to the administration of lansoprazole in 0.9% sodium chloride (approved diluent; see section 5) are reported.

- Lansoprazole inhibits both basal and stimulated gastric acid secretion via selective inhibition of H^+/K^+-adenosine triphosphatase, the enzyme that catalyses the final step in gastric acid secretion in parietal cells.[1]
- Both oral and intravenous lansoprazole suppressed gastric acid output (study 1).[3] Compared with baseline (1.42 and 11.26 mmol/h), both median basal acid output and median maximum acid output (pentagastrin-stimulated) were significantly reduced ($p < 0.001$) after 7 days of treatment with intravenous lansoprazole (0.27 and 5.13 mmol/h) or oral lansoprazole (0.42 and 4.76 mmol/h). Gastric acid output values were equivalent after 7 days of treatment with the oral and intravenous formulations ($p = 0.03$ for equivalence).
- On days 1 and 5 of study 2, the mean intragastric pH over the 24-hour post-treatment period was significantly higher for intravenous and oral lansoprazole than for PEG vehicle ($p \leq 0.05$; JW Freston, personal communication) and did not differ significantly between the intravenous and oral lansoprazole formulations (figure 1).[3]
- Intravenous lansoprazole raised the mean intragastric pH within the first hour of treatment to a significantly ($p \leq 0.05$; JW Freston, personal communication) greater extent than oral lansoprazole or PEG vehicle, on both days 1 and 5 (figure 1).[3]
- Over the 24-hour post-treatment period on days 1 and 5 (study 2), intravenous and oral lansoprazole maintained the pH above 3, 4, 5 and 6 for significantly longer than PEG vehicle ($p \leq 0.05$; JW Freston, personal communication).[3] Over the first hour after treatment, intravenous lansoprazole maintained the pH above 3, 4, 5 and 6 for significantly longer than oral lansoprazole or PEG vehicle ($p < 0.01$).

2. Pharmacokinetic Properties

- In healthy volunteers (studies 1 and 2, see section 1 for study designs), the mean area under the concentration-time curve from 0 to 24 hours (AUC_{24}) and maximum plasma concentration (C_{max}) were numerically higher and mean time taken to reach Cmax (t_{max}) was numerically lower with intravenous lansoprazole (30 mg/day infusion) compared with oral lansoprazole (30mg once daily).[3] In study 1, mean values after multiple doses for the intravenous versus oral formulations were as follows: AUC_{24} 3365 vs 2632 ng • h/mL; C_{max} 1652 vs 807 ng/mL; t_{max} 0.5 vs 1.7 hours. Similar results were

1 The use of trade names is for product identification purposes only and does not imply endorsement.

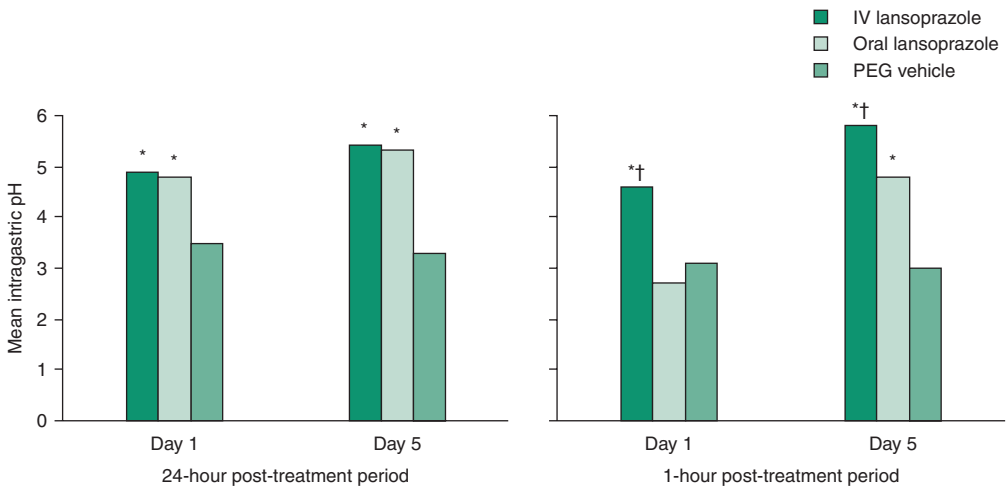

Fig. 1. Intragastric pH after treatment with lansoprazole. In an open-label, crossover study, 36 volunteers received intravenous (IV) lansoprazole (30 mg/day) in 0.9% sodium chloride, oral lansoprazole (30mg once daily) or IV polyethylene glycol (PEG) vehicle for 5 days each.[3] * $p \leq 0.05$ vs PEG; † $p \leq 0.05$ vs oral lansoprazole (JW Freston, personal communication).

seen in study 2: AUC_{24} 3611 vs 3101 ng • h/mL; C_{max} 1884 vs 1052 ng/mL; t_{max} 0.5 vs 1.5 hours.

• The pharmacokinetic parameters following multiple doses in these studies (seven in study 1, five in study 2) were numerically similar to those observed after single doses for both intravenous and oral lansoprazole.[3]

• The mean steady-state volume of distribution and clearance after 7 days of once-daily intravenous lansoprazole were 15.87L and 10.89 L/h (study 1).[3] In both studies, mean elimination half-life ($t_{1/2}$) values following multiple doses were similar with the oral and intravenous formulations and ranged from 1.15 to 1.21 hours.

• Lansoprazole is metabolised in the liver; two metabolites with minimal antisecretory activity have been identified in the plasma.[4] It is thought that lansoprazole is transformed into two active species that inhibit acid secretion in the canaliculi of the parietal cells, but are not present in the systemic circulation. After a single oral dose of lansoprazole, very little unchanged lansoprazole was excreted in the urine. Following an oral dose of [^{14}C]lansoprazole, approximately one-third of the radioactivity was recovered in the urine and approximately two-thirds was recovered in the faeces.

• The pharmacokinetics of intravenous lansoprazole have not been studied in the elderly, children or patients with renal or hepatic impairment. Therefore, the well established pharmacokinetic profile of oral lansoprazole[1] was used to establish the recommended dosages of intravenous lansoprazole for administration in these patients (see section 5).

• According to limited available data, the pharmacokinetic profile of oral lansoprazole is similar in men and women.[4]

3. Therapeutic Efficacy

The efficacy of intravenous lansoprazole in reducing gastric acid output in adults with erosive oesophagitis has been assessed in a double-blind, multicentre, placebo-controlled trial for which results are available in an abstract[5] and are also reported in the manufacturer's US prescribing information.[4] *Helicobacter pylori*-negative patients (n = 87) received once-daily oral lansoprazole (30mg) for 7 days, and then were randomised to receive either once-daily intravenous lansoprazole

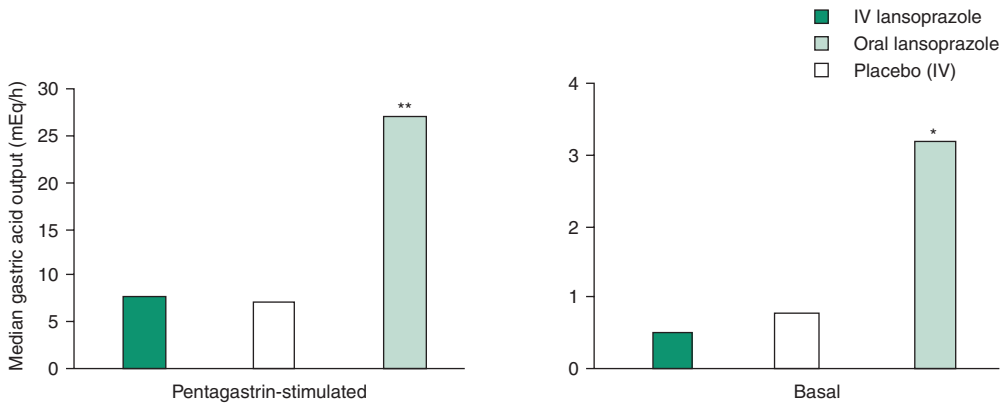

Fig. 2. Gastric acid suppression after 7 days of treatment with intravenous (IV) or oral lansoprazole.[4,5] Eighty-seven *Helicobacter pylori*-negative patients with erosive oesophagitis received once-daily oral lansoprazole (30mg) for 7 days, and then were randomised to receive either once-daily IV lansoprazole (30mg infused over 30 minutes) or IV placebo for 7 days. * $p = 0.005$, ** $p < 0.001$ vs IV lansoprazole.

(30mg, 30-minute infusion) or intravenous placebo for 7 days (intravenous lansoprazole is approved for use for up to 7 days [section 5]). Whether patients were fed or fasting was not stated. Gastric acid output (basal and pentagastrin-stimulated) was measured at the end of oral lansoprazole treatment, and after the first and last days of randomised treatment.

- Intravenous lansoprazole suppressed gastric acid output.[5] After 7 days of treatment, median pentagastrin-stimulated and basal gastric acid output were significantly ($p \leq 0.005$) lower with IV lansoprazole than with placebo (figure 2).[4] Equivalence was shown between median pentagastrin-stimulated gastric acid output levels after 1 and 7 days of intravenous lansoprazole and 7 days of oral lansoprazole (8.2, 7.6 and 7.2 mEq/h; $p < 0.04$ for equivalency).[4,5] Within 48 hours of replacing oral lansoprazole with intravenous placebo there was a significant increase in stimulated gastric acid output (14.5 vs 8.2 mEq/h; $p = 0.002$).[5]

4. Tolerability

Limited tolerability data are available for intravenous lansoprazole. The majority of data in this section are derived from the manufacturer's US prescribing information for intravenous lansoprazole.[4] A brief summary of the tolerability of oral lansoprazole is also included.

- In a randomised, placebo-controlled trial in 87 adults with erosive oesophagitis,[5] intravenous and oral lansoprazole (30 mg/day) were well tolerated and all adverse events were mild or moderate in severity (data reported in an abstract).
- The main treatment-related adverse events (≥1% of patients) were nausea (1.3%), headache (1%), injection-site pain (1%) and injection-site reactions (1%) in four trials in which 161 subjects received intravenous lansoprazole (dosage and whether subjects were healthy volunteers and/or patients with erosive oesophagitis was not reported).[4] Less common treatment-related adverse events included abdominal pain, vasodilatation, diarrhoea, dyspepsia, vomiting, dizziness, paraesthesia, rash and taste perversion.
- The tolerability of oral lansoprazole is well established.[1] Meta-analytic and post-marketing surveillance tolerability data for oral lansoprazole are available for more than 30 000 patients with various acid-related disorders. Oral lansoprazole was generally well tolerated: the most common adverse events included dose-dependent diarrhoea, headache, abdominal pain and nausea/vomiting.[1] After short-term (≤2 months) administration of oral lansoprazole, the incidence of adverse events was generally ≤5%. The

incidence of headache, diarrhoea and nausea was similar in oral lansoprazole (30 mg/day) and omeprazole (20 mg/day) recipients.[1]

5. Dosage and Administration

The approved dosage of intravenous lansoprazole in adults with erosive oesophagitis is 30 mg/day infused over 30 minutes for up to 7 days.[4] Lansoprazole may be diluted in 0.9% sodium chloride, lactated Ringer's solution or 5% dextrose prior to intravenous administration. No dosage adjustments of intravenous lansoprazole are considered necessary in the elderly, or patients with renal insufficiency or mild-to-moderate hepatic insufficiency. Dosage reduction should be considered in patients with severe hepatic impairment.

6. Intravenous Lansoprazole in Erosive Oesophagitis: Current Status

Intravenous lansoprazole is approved in the US for short-term use (up to 7 days) in patients with erosive oesophagitis who are temporarily unable to take oral formulations.[4] It has shown efficacy in reducing gastric acid output in a well controlled trial in this indication and is well tolerated.

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