Safety and Efficacy of Lansoprazole Injection in Upper Gastrointestinal Bleeding: a Postmarketing Surveillance Conducted in Indonesia

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ABSTRACT

Aim: to assess the safety and effectiveness of lansoprazole injection (Prosogan®) in patients with upper gastrointestinal bleeding due to peptic ulcers or erosive gastritis. Methods: this study was a multicenter observational postmarketing study of lansoprazole (Prosogan®) injection. Patients with upper gastrointestinal bleeding due to peptic ulcers or erosive gastritis were given intravenous lansoprazole for a maximum of 7 days or until the bleeding stopped and the patients were able to take oral doses of lansoprazole. Primary outcome of the study was cessation of bleeding. Some laboratory parameters were also measured. Results: among a total of 204 patients evaluable for safety, there was no adverse event reported during the study. A total of 200 patients were eligible for efficacy evaluation, 125 patients (62.5%) were males. Among these patients, upper GI bleeding stopped in 20 patients (10.0%) on day 1, in 71 patients (35.5%) on day 2, 75 patients (37.5%) on day 3, 24 patients (12.0%) on day 4, and 7 patients (3.5%) on day 5, making a cumulative of 197 patients (98.5%) on day 5. The hemostatic
Effect was rated as “excellent” if the bleeding stopped within 3 days, and “good” if the bleeding stopped within 5 days. Thus, the results were “excellent” in 166 patients (83.0%) and “good” in 31 patients (15.5%). These results were not different between males and females, between age below 60 years and 60 years and above, and between baseline Hb below 10 g/dL and 10 g/dL and above. **Conclusion:** the results of this observational postmarketing study in 200 patients with upper gastrointestinal bleeding due to peptic ulcers or erosive gastritis demonstrated that intravenous lansoprazole twice a day was well tolerated and highly effective.

**Key words:** postmarketing surveillance (PMS), lansoprazole, upper gastrointestinal bleeding (UGIB).

**INTRODUCTION**

Upper gastrointestinal bleeding (UGIB) is a severe life-threatening disease with a mortality rate that has remained constant at 5 to 10%, over the past 50 years. Peptic ulcer is the most common cause of UGIB, accounting for about 50% of cases.

Medical treatment of ulcer bleeding is directed to keep the gastric pH above the proteolytic range for pepsin. A rise of the pH of gastric juice to 4 almost completely abolishes the fibrinolytic activity in gastric juice. In keeping the gastric pH above the proteolytic range for pepsin in bleeders, parenteral proton pump inhibitors were demonstrated to be more effective than parenteral histamine H2-antagonists. Lansoprazole injection is the most recent intravenous PPI available in Indonesia. Therefore, it requires a postmarketing study to monitor its safety and effectiveness in clinical practice.

The general objective was to assess the safety and effectiveness of lansoprazole injection in patients with upper gastrointestinal bleeding, due to peptic ulcers or erosive gastritis. The specific objectives were: to assess safety based on the objective and subjective signs and symptoms, and abnormalities of liver function tests and to assess effectiveness of its hemostatic effect.

**METHODS**

**Design and Patients**

This was an observational, multicenter, postmarketing study in patients with upper gastrointestinal bleeding due to peptic ulcers or erosive gastritis receiving intravenous lansoprazole for a maximum of 7 days or until the bleeding stopped and the patients were able to take oral lansoprazole.

Patients recruited were those who came to the emergency room (ER) of a hospital with hematemesis and/or melena, and met the following inclusion and exclusion criteria. A total of 200 patients were planned to be enrolled from 100 internal medicine specialists in Indonesia. Patients with upper gastrointestinal bleeding were considered eligible if they fulfilled the following inclusion criteria: (i) Men or women with upper gastrointestinal bleeding (UGIB) due to peptic ulcers or erosive gastritis, (ii) aged 18 up to 70 years inclusive. Patients were excluded from the study if they were hemodynamically unstable (hypotension, tachycardy, or postural changes in heart rate or blood pressure), hypersensitive to lansoprazole or other PPIs, patients with liver cirrhosis, pregnancy or lactation, patients suffering from gastrointestinal cancer or receiving atazanavir sulfate.

**Study Drug**

Eligible patients received lansoprazole injection 30 mg mixed with 0.9% NaCl or 5% glucose solution and administered by i.v. drip twice a day, or lansoprazole injection 30 mg mixed with 20 mL of 0.9% NaCl or 5% glucose solution and administered by slow i.v. injection twice a day, for a maximum of 7 days.

**Procedure**

Upon arrival at the ER, anamnesis and physical examination were performed, and also measurement of blood chemistry (complete blood count, SGPT, SGOT, creatinine, ureum). To patients who were hemodynamically stable with normal blood pressure, intravenous lansoprazole was given twice a day for a maximum of 7 days or until the bleeding stopped and the patients were able to take oral lansoprazole. Routine upper GI endoscopy was performed in order to confirm cause of bleeding.
If the UGIB was not caused by peptic ulcers or erosive gastritis, these patients were not included in the efficacy population, but included in the safety population. The bleeding stopped if there was no more hematemesis (the nasal tube fluid was already clear) and/or melena (the stool was not black and liquid anymore). Hemoglobin level was monitored daily depending on the patient condition. Vital signs and blood chemistry were measured again on the last day of therapy. Concomitant medication was recorded, with the respective indications. Objective and subjective signs and symptoms which emerged during intravenous lansoprazole administration were recorded.

Serious adverse events (AE) were noted: death, life-threatening, requires/prolongs hospitalization, results in persistent/significant disability/incapacity, a congenital anomaly/birth, requires intervention to prevent one of the above or may expose the patient to danger. All serious adverse events had to be reported to the sponsor within 24 hours (1 working day). A special form was made available to be filled in by the investigator, with monitoring doctor’s help.

Data Analysis

Safety analysis. All adverse events were listed, and also AEs which were probably and possibly related to lansoprazole injection.

Efficacy analysis. Efficacy of lansoprazole injection was evaluated in UGIB patients due to peptic ulcers or erosive gastritis who did not require endoscopic hemostasis. In these patients, the hemostatic effect of lansoprazole injection was evaluated every day until a maximum of 7 days of treatment and the percentage of patients whose bleeding stopped was calculated. The hemostatic effect was determined and rated as excellent, good, fair or poor as follows. Excellent: if the bleeding stopped within 3 days. Good: if the bleeding stopped within 5 days. Fair: if the bleeding stopped within 7 days. Poor: if the bleeding did not stop within 7 days, or the treatment was changed.

RESULTS

During the study from December 2010 until December 2011, 204 patients were screened, total patients evaluable for safety were 204, while total patients evaluable for efficacy were 200 (4 patients did not meet the inclusion criteria: 3 patients aged <18 years, 1 patient was GERD patient).

Patient demographics and baseline characteristics are shown in Table 1, vital signs in Table 2, medical history in Table 3, and blood chemistry in Table 4.

![Table 1. Patient demographics and baseline characteristics](image1)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean (SD)</th>
<th>Median (Range)</th>
<th>Missing</th>
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<tbody>
<tr>
<td>Male: n (%)</td>
<td>125 (62.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>52.1 (13.34)</td>
<td>55.0 (19 – 70)</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>60.8 (10.39)</td>
<td>60.0 (36 – 100)</td>
<td>1</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.0 (3.54)</td>
<td>23.0 (14 – 34)</td>
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![Table 2. Vital signs](image2)

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Mean (SD)</th>
<th>Median (Range)</th>
<th>Missing</th>
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</thead>
<tbody>
<tr>
<td>SBP (mm Hg)</td>
<td>123.1 (18.02)</td>
<td>120.0 (90–180)</td>
<td>-</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>77.6 (9.77)</td>
<td>80.0 (50–100)</td>
<td>-</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>89.5 (10.66)</td>
<td>88.0 (69–124)</td>
<td>1</td>
</tr>
<tr>
<td>Respiratory rate (per min)</td>
<td>20.0 (3.02)</td>
<td>20.0 (14–31)</td>
<td>3</td>
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<tr>
<td>End of the study (day 7)</td>
<td></td>
<td></td>
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<tr>
<td>SBP (mm Hg)</td>
<td>121.9 (12.89)</td>
<td>120.0 (90–190)</td>
<td>1</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>78.4 (7.46)</td>
<td>80.0 (60–100)</td>
<td>1</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>83.7 (8.01)</td>
<td>82.0 (68–124)</td>
<td>1</td>
</tr>
<tr>
<td>Respiratory rate (per min)</td>
<td>19.5 (3.10)</td>
<td>20.0 (14–36)</td>
<td>1</td>
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</tbody>
</table>

Patients were mostly males (62.5%), mean age was 52.1 years, and mean BMI was 23.0.

Systolic as well as diastolic blood pressure did not change during the study.

Patient medical history consisted of gastrointestinal diseases such as erosive gastritis (40.5%), gastric ulcer (26.5%), and duodenal ulcer (12.0%), and the patients also suffered from some comorbid diseases such as diabetes mellitus, hypertension, coronary artery disease, dyslipidemia, and others.
Laboratory findings showed that during treatment with lansoprazole injection, hemoglobin level increased. At baseline, hemoglobin level was 9.9 g/dL and rose to 10.9 g/dL after treatment with lansoprazole injection. Other laboratory parameters were also examined in this study. During one week lansoprazole injection, liver function tests (ALT and AST) did not change. Kidney function, as shown by creatinine and BUN, were improved (from an average of 37.9 to 35.4 mg/dL and from a mean of 1.2 to 1.1 mg/dL, respectively) during treatment with lansoprazole injection.

Peptic ulcer was diagnosed endoscopically in 104 patients (54%) and erosive gastritis in 96 patients (46%).

In this study, 92 patients were given lansoprazole as intravenous drip and 97 patients as intravenous slow injection, while 11 patients were given a combination of both.

**Safety Analysis (n=204)**

No adverse events probably or possibly related to lansoprazole injection was were reported during the study.

**Efficacy Analysis (n=200)**

Number and percentage of patients whose UGIB stopped during treatment with lansoprazole injection are shown in Figure 1. Hemostatic effects of lansoprazole injection and hemostatic effects based on gender, age groups, and Hb groups are shown in Table 6.
This study showed that lansoprazole injection could stop bleeding in 10% of cases on day 1, and on day 3 the cumulative stopped bleeding rate was 83%, increasing to 99.5% after 7 days of treatment.

The hemostatic effects of lansoprazole injection based on gender were not different (Kolmogorov Smirnov test: Z = 0.183, p = 1.0).

Based on age groups (<60 years and >60 years) the hemostatic effects of lansoprazole injection were also not different (Kolmogorov-Smirnov test: Z=0.594, p=0.87), neither the hemostatic effects of lansoprazole injection based on Hb groups at baseline (Kolmogorov-Smirnov test: Z=0.521, p=0.95).

**DISCUSSION**

In the present study, it was found that 104 cases (52%) of the 200 UGIB cases were due to peptic ulcer and 96 cases (48%) to erosive gastritis. Many studies have shown that 50% of the UGIB cases were caused by peptic ulcer. Research conducted at Cipto Mangunkusumo Hospital that analyzed patients who presented with upper gastrointestinal bleeding, found that 50% were caused by peptic ulcer and erosive gastritis.

The mortality rate associated with UGIB remained unchanged around 5-10% for the past 50 years, despite continuing improvement in the diagnostic and therapeutic modalities. This unchanged mortality rate may be accounted by age and prevalence of concurrent illness, both are important predictors of death, that continue to rise among patients with UGIB. Patients with bleeding usually die not from exsanguination, but from decompensation due to other diseases.

Appropriate initial management is one of the key success to reduce morbidity and mortality. In general, causes of gastrointestinal bleeding were variceal or non-variceal. A systematic review and meta-analysis of 21 randomized controlled trials comparing 2915 patients (up to February 2003) showed that proton pump inhibitor treatment reduced rebleeding (OR=0.46; 95% CI=0.33-0.64) and the requirement for surgery (OR=0.59; 95% CI=0.46-0.76) after ulcer bleeding but did not reduce mortality (OR=1.11; 95% CI=0.79-1.57).

Whittle et al. have shown that, unlike in the skin or vasculature, platelet aggregation plays a minimal role in the initial hemostatic events in the gastric mucosa and that the arrest of gastric hemorrhage is brought about largely by processes primarily involving the coagulation system.

The stronger drugs suppressing acid production, the better in stopping the gastrointestinal bleeding. Proton pump inhibitors raise the pH to about 6.9 The target therapeutic goal is to achieve an intragastric pH above 6, at which the clotting process is optimal and any formed clot is stabilized. The success of hemostasis is highly dependent on the intragastric pH and studies have shown that, when the intragastric pH is low, platelet function is impaired and pepsinogen is activated to pepsin, which disaggregates platelet plugs.

<table>
<thead>
<tr>
<th>Table 5. Hemostatic effects: total and based on gender</th>
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<tbody>
<tr>
<td><strong>Hemostatic effect</strong></td>
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<tr>
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<tr>
<td>Excellent (bleeding stopped within 3 days)</td>
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<tr>
<td>Good (bleeding stopped within 5 days)</td>
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<tr>
<td>Fair (bleeding stopped within 7 days)</td>
</tr>
<tr>
<td>Poor (bleeding did not stopped within 7 days)</td>
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<tr>
<td>Total</td>
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<th>Table 6. Hemostatic effects based on age group and hemoglobin level at baseline</th>
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<tr>
<td><strong>Hemostatic effect</strong></td>
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<tr>
<td>-----------------------</td>
</tr>
<tr>
<td>Excellent</td>
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<td>Good</td>
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<td>Fair</td>
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<td>Poor</td>
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<tr>
<td>Total</td>
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A meta-analysis of 27 randomized trials of H2-receptor antagonists in over 2500 patients with acute UGIB suggested that the drugs reduced the rates of rebleeding, surgery and mortality, by about 10, 20, and 30%, respectively, notably among those with gastric ulcers. In a meta-analysis comparing proton pump inhibitors with H2 antagonists, it was found that persistent or recurrent bleeding was less frequent with proton pump inhibitors (6.7) than with H2 antagonists (13.4%) (OR 0.4; 95%CI: 0.27-0.59). The need for surgery and mortality rates did not reach statistical significance but showed a favorable trend towards PPIs.

Mucosal fibrinolytic activity is enhanced in patients with bleeding gastrointestinal ulcers. Acid suppressive therapy reduced this increased activity and ultimately decreased bleeding in peptic ulcers.

This post-marketing survey showed that lansoprazole injection could stop upper GI bleeding in 10% of cases on day 1, and 83% of the upper GI bleeding stopped on day 3, increasing to 99.7% after 7 days of treatment. This indicates that lansoprazole injection works quickly to stop bleeding. The hemostatic effect was rated as excellent if the bleeding stopped within 3 days. Accordingly, this drug was excellent for as much as 83%. These findings suggest that lansoprazole may be useful in situations where rapid acid control is required, such as in emergency care situations.

A preliminary study using intravenous lansoprazole 30 mg bid in patients with UGIB for 7 days showed that bleeding was arrested in 16 of 18 patients (89%) within 3 days.

A previous study using oral omeprazole 40 mg bid vs. placebo in patients with bleeding peptic ulcers for 5 days showed that omeprazole therapy was associated with significant reductions in the rates of further bleeding (10.9% vs. 36.4%) and surgical intervention (7.2% vs. 23.6%), and the need for transfusion (29.1% vs. 70.9%). Another study with bolus i.v. (80 mg) followed by infusion (8 mg/h) of omeprazole vs. placebo for 72 hours in severe ulcer hemorrhage after endoscopic therapy showed that omeprazole reduced the number of operations (5.4% vs. 11.1%), endoscopic treatments (4.6% vs. 11.1%), and the duration and severity of bleeding (18.0% vs. 31.4% with moderate or severe bleeding).

Bolus i.v. (80 mg) followed by infusion (8 mg/h) of omeprazole for 3 days in patients with bleeding peptic ulcers after endoscopic treatment was also studied by Lau et al. and showed that omeprazole reduced the risk of recurrent bleeding (6.7% vs. 22.5% within 30 days; HR=3.9).

A recent prospective study conducted by Liang et al. showed that high-dose pantoprazole infusion therapy following endoscopic hemostasis treatment is not superior to low-dose PPI therapy in terms of reducing rebleeding among low risk patients with a bleeding peptic ulcer (11.1% in each group). A review by van Rensburg and Cheer concludes that intravenous pantoprazole is an effective option in the treatment of UGIB, the prevention of rebleeding, and for the prophylaxis of acute bleeding stress ulcers.

A meta-analysis of 24 randomized controlled trials (4373 participants) through November 2004 on the efficacy of PPIs for peptic ulcer bleeding showed that treatment with PPIs did not reduce mortality (OR=1.01) but significantly reduced rebleeding (OR=0.49; 95% CI=0.37-0.65) and the need for surgery (OR=0.61; 95% CI=0.48-0.78). Treatment with PPIs significantly reduced mortality in Asian trials (OR=0.35; 95% CI=0.16-0.74) and in patients with active bleeding or a nonbleeding visible vessel (OR=0.53; 95% CI=0.31-0.91). This meta-analysis was the extension of the previous one, involving 50% more patients, giving the same results.

In this survey, hemoglobin was also evaluated. During treatment with lansoprazole injection, hemoglobin level increased. At baseline, hemoglobin level was 9.9 g/dL and rose to 10.9 g/dL after treatment with lansoprazole injection. These data demonstrated that during administration of lansoprazole, gastrointestinal bleeding did not occur, clinically as well as in the laboratory. In several studies, low hemoglobin value is one predictor of rebleeding.

Several laboratory parameters were also examined in this study. The use of lansoprazole injection for 1 week did not affect liver function. Kidney function (creatinine and BUN) was
improved during treatment with lansoprazole injection and these conditions were in line with the cessation of gastrointestinal bleeding.

CONCLUSION

The results of this observational postmarketing study in 200 patients with endoscopically confirmed upper gastrointestinal bleeding due to peptic ulcers or erosive gastritis demonstrated that intravenous lansoprazole twice a day was well tolerated and highly effective.

The authors declare that they have no conflicts of interest in relation to this manuscript.

ACKNOWLEDGMENTS

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CONFLICT OF INTEREST

The authors received grant support from PT. Takeda Indonesia.

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