EFFICACY AND SAFETY OF INTRAVENOUS S-PANTOPRAZOLE IN THE TREATMENT OF MODERATE TO SEVERE GASTROESOPHAGEAL REFLUX DISEASE (GERD) AND/OR PEPTIC ULCERS

Suresh Jain*[a], Jayprakash Rathi[b]

[a]Digestive Endoscopy Clinic & A Day Care Center, Pune-411011 (India) (drjainsuresh@gmail.com) *Author for correspondence; [b]Remedy Hospital, Ramanand Complex, Pune-Solapur Road, Hadapsar, Pune-411028 (India).

Summary

This was an open-label, non comparative study to assess efficacy and safety of intravenous (IV) S-Pantoprazole in the treatment of patients with peptic ulcers and/or moderate to severe gastroesophageal reflux disease (GERD), in clinical setting. Men or non-pregnant women at least 18 years of age who presented clinically with acute symptoms (viz. pain, heartburn, regurgitation, nausea and vomiting) suggestive of moderate to severe GERD and/or severe peptic ulcers that required use of IV proton pump inhibitor (PPI) or patients with endoscopic esophagitis (grade II-III) and/or severe peptic ulcers (confirmed by endoscopy as visible ulcer/erosion/oozing/bleeding in any form), were enrolled after applying the inclusion and exclusion criteria and after obtaining written informed consent. Upper gastrointestinal endoscopy, total and differential white blood cell (WBC) count, platelet count, blood urea, hemoglobin and faeces examination was done at baseline. Each enrolled patient was given S-Pantoprazole IV for 3 days. The visual analog scale (VAS) (0-100) was used to assess severity of symptoms. A total of 50 patients (M: F: 35: 15, age (mean ± SD): 44 ± 16 yrs) were enrolled and all completed the study. Patients received IV S-Pantoprazole 20 mg (solution was prepared by injecting 10 ml of 0.9% sodium chloride injection into the vial containing the lyophilised powder and this freshly prepared solution was further diluted with 100 ml of 0.9% sodium chloride injection to administer as a short-term infusion) once daily for three days. There was a significant ($P<0.001$, T-test) improvement in symptoms of heartburn, regurgitation, pain, nausea and vomiting after three days of therapy. 100% patients showed $\geq$50% relief from heartburn and regurgitation and 94% of the patients showed $\geq$50% relief from pain after three days of therapy with S-Pantoprazole 20 mg IV. S-Pantoprazole IV was also well-tolerated. Headache, constipation, flatulence and diarrhea were seen in 5, 3, 6 and 9 patients respectively. However, these were mild in nature and were not attributable to therapy in the opinion of the investigators. Thus S-Pantoprazole IV at half the dose of racemate was found to be an effective and safe PPI option for patients with peptic ulcer and/or moderate to severe GERD.

Keywords: S-Pantoprazole, Intravenous, Efficacy, Safety

Introduction

Intravenous PPIs improve the management of patients with conditions in which rapid reduction of gastric acid output is desirable. For example, they may help in the management of patients with bleeding ulcers by fostering acid-base conditions that allow for more rapid clot organization and stabilization and further helps prevent re-bleeding. Also patients who develop an acute exacerbation of GERD, or are unable to use enteral therapy due to an underlying medical condition, may require a change to IV therapy. Using IV PPI, pH levels > 6 may be rapidly achieved and maintained with an IV bolus dose followed by continuous infusion. The continuous infusion is necessary to inhibit newly generated proton pumps and thereby maintain a nearly neutral gastric milieu.[1]

Pantoprazole is a potent inhibitor of gastric acid secretion. Animal and in vitro studies have demonstrated it to be comparable to or more potent than omeprazole, with less potential for interactions with P450 cytochromes and better acid stability. Pantoprazole is available in form of oral and IV formulation. IV pantoprazole is indicated in patients with GERD, Zollinger-Ellison syndrome, and peptic ulcers. IV infusion of pantoprazole produces a faster and steadier acid suppression than an oral regimen. Furthermore, some patients with severe erosive esophagitis cannot take pills by mouth and will benefit from an IV formulation. It is also observed that healing takes place in severe erosive esophagitis with continuous IV pantoprazole in just 3 days. Comparative pH studies have proved superiority of IV pantoprazole in raising intragastric pH than H2-receptor antagonists.[2, 3]

Pantoprazole, however is a racemic mixture of S-Pantoprazole and R(+)Pantoprazole in 1:1 ratio. The pharmacokinetics of R and S isomers of Pantoprazole vary widely in extensive and poor metabolizers. Studies have shown that S-Pantoprazole is more potent (1.5 to 1.9 times) and more effective (3 to 4 times) than the racemate in inhibiting gastric lesions in different pre-clinical models, suggesting that in patients, S-Pantoprazole at 50% of the dose of racemate would be at least equivalent in efficacy to racemate. This was further confirmed by results of a multicentric, comparative clinical trial of S-Pantoprazole versus racemic Pantoprazole in patients with GERD which showed superior efficacy with S-Pantoprazole 20 mg compared to racemic Pantoprazole 40 mg.[4]

Present study was conducted to assess the safety and efficacy of IV S-Pantoprazole in the treatment of patients with peptic ulcers and/or moderate to severe GERD.

Materials and methods

This was an open-label, non comparative study in clinical setting conducted in compliance with the 'Guidelines for Clinical Trials on Pharmaceutical Products in India-GCP Guidelines' issued by the Central Drugs Standard Control Organization, Ministry of Health, Government of India (http://www.cdsco.nic.in/html/GCP1.html). The Ethical Committee

Approval was taken from Independent Ethics Committee (Kotbagi Hospital, Pune, India) for all the investigators.

S-Pantoprazole IV (20 mg/vial) manufactured by Emcure Pharmaceuticals Ltd, Pune (India) was used as study medication. Said medication was provided by Emcure Pharmaceuticals Ltd, Pune (India) in the form of vials, each vial containing 20 mg of S-Pantoprazole.

Study population

Study population comprised of – men or non-pregnant women at least 18 years of age who presented clinically with acute symptoms (viz. pain, heartburn, regurgitation, nausea and vomiting) suggestive of moderate to severe GERD and/or severe peptic ulcers that required use of IV PPI or patients with endoscopic esophagitis (grade II-III) and/or severe peptic ulcers (confirmed by endoscopy as visible ulcer/erosion/oozing/bleeding in any form), patients who themselves or their legally authorized representatives were capable of understanding or giving written informed consent before the study and patients who had a high probability for compliance and completion of the study. The decision to use an intravenous PPI was based on the acuteness of the condition presenting to the physician who would decide need to suppress acid secretion though an IV PPI.

Patients with esophagitis other than reflux esophagitis, such as infectious esophagitis and esophageal cancer; patients with a history of glaucoma in either eye, history of any intraocular eye surgery within preceding 3 months, history of/or presence of signs of optic nerve swelling, history of acute change in vision or vision loss in either eye; patients with any malignancy (except skin cancer) which required therapy within the last 6 months; patients with significant liver/kidney/heart/lung diseases or sepsis/airway intubation; patients with history of allergy to any proton-pump inhibitor (PPI) including pantoprazole or patients with prior administration of any PPI (within 72 hours) or histamine-2 receptor antagonist (within previous 24 hours) of study enrolment; patients with known human immunodeficiency virus infection and/or hepatitis B virus infection, organ transplantation and patients without the ability to comply with the study protocol and complete the study in the judgment of the investigator were excluded from the trial.

Interventions

Patients fulfilling inclusion and exclusion criteria were enrolled in the study. Upper gastrointestinal endoscopy and laboratory investigations (blood urea, faeces examination, haemoglobin, platelet count, total and differential WBC count and serological tests for HIV and hepatitis B virus infection) were done at the baseline (before therapy).

Each enrolled patient was given S-Pantoprazole IV for 3 days. The dosage was one vial of 20 mg S-Pantoprazole i.v. per day. A ready-to-use intravenous solution was prepared by injecting 10 ml of 0.9% sodium chloride injection into the vial containing the lyophilised powder. This freshly prepared solution was administered intravenously over 2 to 15

minutes, either as a slow injection or by further diluting it with 100 ml of 0.9% sodium chloride injection or 5% glucose injection (and administered as a short-term infusion).

Laboratory investigations and or endoscopy was repeated after three days in case of suspected re-bleeding. Patients were switched to oral S-Pantoprazole after 3 days of IV therapy.

Recording of study variables

Patients were asked to mark the severity of their symptoms (heartburn, regurgitation, pain, nausea and vomiting) on a visual analogue scale (VAS) of 0 mm to 100 mm, at each visit. The VAS severity score was then quantified by the physician at every visit. Monitoring of safety parameters was done for 3 days. Serious adverse event form was used for recording of serious adverse event.

Assessment of efficacy & safety

To assess efficacy of study medications, improvement in VAS scores of symptoms viz. heart-burn, regurgitation, pain, nausea and vomiting on day 3 of the therapy was compared with baseline values. Proportions of patients showing complete or $\geq$50% relief of their symptoms after therapy was also assessed. Patients were evaluated clinically every day of therapy for drug-induced adverse effects. Tolerability profile of study medication was assessed by evaluating incidence of possible drug-related adverse effects.

Statistical analysis

Paired T test was applied to assess improvement of VAS symptom scores and Chi-square test was applied for proportion of patients showing $\geq$50% relief in symptoms. All the treatment comparisons were two-sided tests using $P<0.05$ significance level. The GraphPad InStat software was used for statistical analyses.

Results

A total of 50 patients completed the study. The baseline characteristics of these patients, the endoscopic diagnoses and baseline laboratory parameters are provided in Table 1, Table 2, and Table 3 respectively.

Table 1. Baseline characteristics of patients (n = 50)

Total number of patients enrolled, n=	50
Total number of patients who completed study, n=	50
Age (yrs, mean ± SD)	44 ± 16
Weight (Kg, mean ± SD)	58.6 ± 8.34
Male: Female (ratio)	2.33: 1
Systolic blood pressure, SBP (mmHg, mean ± SD)	123.9 ± 10.2
Diastolic blood pressure, DBP (mmHg, mean ± SD)	82.2 ± 6.8
Heart rate, HR (per minute, mean ± SD)	88.2 ± 11.1
Clinical diagnosis	
Moderate to severe GERD, n=	37
Severe peptic ulcer, n=	13
Other significant history (in addition to inclusion criteria)	
Smokers, n=	7
Symptoms of nocturnal GERD, n=	34
History of NSAID induced gastritis, n=	6

Table 2. Endoscopic diagnoses (n=50)

Esophageus		
Grade II to III GERD, n=		16
Esophagitis, n=		2
Esophageal ulcers, n=		2
Varices, n=		2
Hiatus hernia, n=		4
Stomach		
Moderate to severe gastritis, n=39	Pangastritis, n=	18
	Antral gastritis, n=	12
	Fundic gastritis, n=	1
	Billiary gastritis, n=	1
	Atrophic gastritis, n=	1
	Only gastritis, n=	6

Table 3. Baseline laboratory parameters

Parameters		**Observed values (mean ± SD)**	**Normal values (range)**
Blood urea (mg %)		23.6 ± 6.5	Up to 50
Platelet Count (lac/mm^3)		2.1 ± 0.2	1.5-3.5
Total WBC count (/mm^3)		8,218 ± 1730.6	4,0000-11,000
Differential WBC count	Neutrophils (%)	70.3 ± 9.6	40-75%
	Eosinophils (%)	1.8 ± 2.4	0-4%
	Basophils (%)	0	0-1%
	Lymphocytes (%)	26.3 ± 8.2	20-45%
	Monocytes (%)	1 ± 1	2-8%
Hemoglobin (gm %)		12.5 ± 2.6	M: 13.5-16.5 F: 11.5-14.5
Faeces examination findings			
No abnormality detected, n=		48	
Occult blood positive, n=		2	

There was a significant (P<0.001, T-test) improvement in symptoms of heartburn, regurgitation, pain, nausea and vomiting after three days of therapy (Table 4).

Table 4: Analysis of Visual Analog Scale (VAS) symptom scores (mean ± SD), n=50

	Baseline (Day 0, before therapy)	**Day 3 (After therapy)**	**P-value (T-test)**
Pain	43.6 ± 20.8	14.3 ± 11	<0.0001
Heartburn	36.5 ± 28.4	10.9 ± 9.6	<0.0001
Regurgitation	6.3 ± 11.1	0.7 ± 2.5	<0.0001
Nausea	32.5 ± 21.7	4.6 ± 7.7	<0.0001
Vomiting	12.5 ± 17.8	0.8 ± 2.7	<0.0001

Proportion of patients who showed ≥50% relief from symptoms is provided in Table 5.

Table 5: Analysis of proportion (%) of patients with symptoms

	Baseline (before therapy) n, with symptoms	**Day 3 (after therapy) n (%), with ≥ 50 % improvement in baseline symptoms**
Pain	50	47 (94%)
Heartburn	39	39 (100%)
Regurgitation	14	14 (100%)
Nausea	42	40 (95.2%)
Vomiting	21	21 (100%)

Headache, constipation, flatulence and diarrhea were seen in 5, 3, 6 and 9 patients respectively (Table 6). However, these were mild in nature and were not attributable to therapy in the opinion of the investigators.

Table 6: Assessment of safety, n=50

Adverse drug reaction (ADR) (n)	Severity of ADR	Causally linked to S-Pantoprazole IV in the opinion of Investigator	Incidence reported with Pantoprazole IV [5]
Headache (n=5)	Mild	No	> 1%
Constipation (n=3)	Mild	No	> 1%
Diarrhea (n=9)	Mild	No	> 1%
Flatulence (n=6)	Mild	No	> 1%

Discussion

Present study showed that 100% patients showed ≥50% relief from heartburn and regurgitation and 94% of the patients showed ≥50% relief from pain after three days of therapy with S-Pantoprazole 20 mg IV. S-Pantoprazole IV was also well-tolerated. Studies conducted with racemic Pantoprazole IV in moderate to severe GERD patients have shown similar results after 5-7 days of treatment.

In a study in endoscopically diagnosed moderate or severe GERD (stage II and III) patients, patients were treated once daily with 40 mg pantoprazole administered as an intravenous injection for the initial 5-7 consecutive days. These patients were then given Pantoprazole tablet, for up to 8 weeks. The results showed that complete healing was achieved in 87% and 95% patients, after 4 and 8 weeks, respectively. After 2 weeks of treatment, heartburn, acid regurgitation, and pain resolved in 97%, 98%, and 100% of the per-protocol patients, respectively. Faster healing was observed in non-smokers, those infected with Helicobacter pylori, and those with initial GERD stage II. This study concluded that Pantoprazole (40 mg), applied as an intravenous-oral regimen to patients with GERD led to fast resolution of symptoms and high healing rates and thus for patients, temporarily unable to take oral medications, this regimen offers safe and reliable gastric acid suppression and allows the possibility of changing between the oral and intravenous administration without the need for dose adjustment.[6]

A study to assess the ability of Pantoprazole IV to maintain gastric acid suppression in patients with GERD who were switched from an oral Pantoprazole formulation to IV formulation, no difference in acid suppression ability was observed in both the formulations. This study thus showed that IV Pantoprazole offers an alternative for gastroesophageal reflux disease patients who are unable to take the oral formulation.[6] Another study conducted to evaluate safety and efficacy of IV pantoprazole when used as initial therapy in patients with GERD and a history of erosive esophagitis showed similar results.[8]

Although present study had certain limitations in terms of open-label design and small sample size, present study has shown that an IV formulation of S-Pantoprazole is an effective and safe IV PPI option in the treatment of patients requiring immediate suppression of gastric acidity and fast relief of their symptoms. As S-Pantoprazole has been shown to provide consistent pharmacokinetics irrespective of metabolizer status, safety of administration in poor metabolisers, higher potency for cytoprotective effect, superior clinical efficacy, and lower interaction potential compared to racemate, [9] an IV formulation of S-Pantoprazole at half the dose of the racemate will be a desirable alternative to IV Pantoprazole.

Conclusions

In clinical settings, S-Pantoprazole IV at half the dose of racemate is an effective and safe PPI option for patients with peptic ulcer and/or moderate to severe GERD. It can be used for initial therapy instead of oral therapy to provide rapid symptomatic improvement. It can also be used in such patients who are unable to take oral therapy with PPIs.

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