POST-MARKETING SURVEILLANCE STUDY TO ASSESS S-PANTOPRAZOLE INDUCED CLINICAL EFFECTIVENESS (SPICE-Study)

Suresh Jain*[a], Jayprakash Rathi[b]
on behalf of SPICE-Study Group, India

[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

We present data from a post marketing surveillance (PMS) study conducted to assess the safety and efficacy of S-Pantoprazole 20 mg tablets in patients with gastroesophageal reflux disease (GERD) and/or peptic ulcers. This was an open label, non-comparative, post-marketing surveillance study performed in clinical settings. Patients of either sex >18 years of age with a diagnosis of acid peptic diseases were enrolled in this study. Data of 280 patients (169 males; 111 females) from 103 centers across India was analyzed. Significant reduction was seen in the mean frequency and mean severity of symptoms as experienced by the patient ($p<0.0001$, Chi-Square test). Significant proportion of patients experienced ≥50% reduction in symptom frequency and severity of heart burn, regurgitation, bloating, nausea, epigastric pain, abdominal pain before meals and abdominal pain after meals ($p<0.0001$). S-Pantoprazole was well tolerated and no patient discontinued therapy for adverse events. S-pantoprazole is an effective and safe proton pump inhibitor for the tratement of GERD, duodenal ulcer (DU) and gastric ulcer (GU).

Key words: S-Pantoprazole, Pantoprazole, Efficacy, Safety

Introduction

Acid peptic disorders (APDs) include a diverse spectrum of disorders whose exact pathophysiology is uncertain. However, they are commonly associated with chronic mucosal damage as a result of excess gastric acid secretion or reflux of acidic gastric contents into the esophagus. The two well defined syndromes of acid peptic disease include the commonly occuring GERD and peptic ulcers (gastric and duodenal). GERD is a complex of chronic symptoms produced by the esophageal mucosal damage inflicted by reflux of acidic gastric contents into the esophagus. Pathophysiological mechanisms

possibly associated with GERD include incompetence of the lower esophageal sphincter (LES) or transient relaxation of LES. GERD is characterized by heartburn or acid reflux which may exacerbate after meals or in supine position.

Proton-pump inhibitors (PPIs) occupy a prominent place in the management of APDs. These drugs act by inhibiting the last step of acid secretion i.e. the H+/K+ - ATPase or the proton pump. Pantoprazole sodium is a proton pump inhibitor. Pantoprazole is the first PPI to become available in both oral and an intravenous preparation. Pantoprazole has been evaluated in more than 100 clinical trials involving more than 11,000 patients. It is effective in treating erosive esophagitis and duodenal and gastric ulcers. It is also effective as adjunctive treatment with antimicrobials in patients infected with Helicobacter pylori. Pantoprazole has been shown to control acid production in Zollinger-Ellison syndrome. Pantoprazole is also a very well tolerated PPI .[1]

S-pantoprazole is the chirally pure form of pantoprazole. S(-)pantoprazole provides 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.[2]

Present study was conducted to assess the safety and efficacy of S-Pantoprazole 20 mg tablets in patients with GERD and/or peptic ulcers.

Materials and methods

This was an open label, non-comparative, post marketing surveillance (PMS) study performed in clinical settings. Patients of either sex above 18 years of age with a history of and/or a confirmed endoscopic diagnosis of GERD or duodenal ulcer or gastric ulcer were enrolled in the trial and were prescribed one tablet of 20 mg S-Pantoprazole (Zosecta, manufactured by Emcure Pharmaceuticals Ltd) daily for 28 days. Patients with hypersensitivity to pantoprazole; patients receiving other anti-GERD medications concurrently; patients with impairment of hepatic/renal/endocrine functions; pregnant/breastfeeding women; patients with suspected poor compliance or those patients who in the opinion of the doctor were not eligible for study participation were excluded from the study. Efficacy was assessed by noting the reduction in the symptom scores of GERD/duodenal ulcer/gastric ulcer on day 28 as compared with the baseline scores. Frequency of symptoms and their severity was graded on a scale of 0-4 (0=absent/none; 1=occasional; 2=frequent/moderate; 3=very frequent/ severe; 4= very severe) at the baseline (day 0) and after 14 and 28 days of therapy with S-Pantoprazole. Safety variables included percentage of adverse events.

Student's T test, Chi-square test and 90% confidence interval analysis was done as appropriate. GraphPad and Confidence Interval Analysis (CIA) software were used for statistical analysis. A P value of less than 0.05 was considered as statistically significant.

Results

A total of 280 patients (169 males; 111 females) completed the study. The demographic characteristics of the study population are provided in Table 1.

Table: 1. Baseline variables

N=	280
M:F	169: 111
Age in years (mean ± SD)	42.61 ±13.66
Weight in kg (mean ± SD)	58.92 ± 10.25
Height in cm (mean ± SD)	159.92 ± 12.08

One hundred and eighty one patients were clinically diagnosed to have GERD of which 17 were endoscopically diagnosed as known GERD patients. Of 53 and 46 patients with clinical diagnoses of duodenal and gastric ulcers respectively, 22 and 21 were endoscopically diagnosed as known cases of duodenal and gastric ulcers respectively. Mean duration of symptoms for GERD, duodenal ulcers and gastric ulcers was 304.07± 401.20 days; 268.27 ± 407.37 days and 138.79 ± 101.87 days respectively. Forty six patients had a history of chronic ingestion of NSAIDs with a mean duration of 250.63 ± 396.46 days as shown in Table 2.

Table 2: Associated habits/ disorders

History of GERD (n)	181
History of duodenal ulcer (n)	53
History of gastric ulcer (n)	46
History of smoking (n)	95
History of alcohol (n) ingestion	38
History of caffeine (>5 cups of coffee/day) ingestion (n)	104
History of prolonged ingestion of NSAIDs (n)	46
Duration of NSAID intake (days; mean ± SD)	250.63 ± 396.46
History of NSAID induced gastritis (n)	64
History of treatment for GERD (n)	161
Duration of previous treatment for GERD (days; mean ± SD)	89.62 ± 171.93

Improvement in the symptom frequency and severity are shown in Figures 1 and 2 respectively. Significant reduction was seen in the mean frequency and mean severity of symptoms as experienced by the patients ($p<0.0001$; T-test; Figure 1, 2).

Figure 1: Improvement in the mean scores for symptom frequency over 28 days

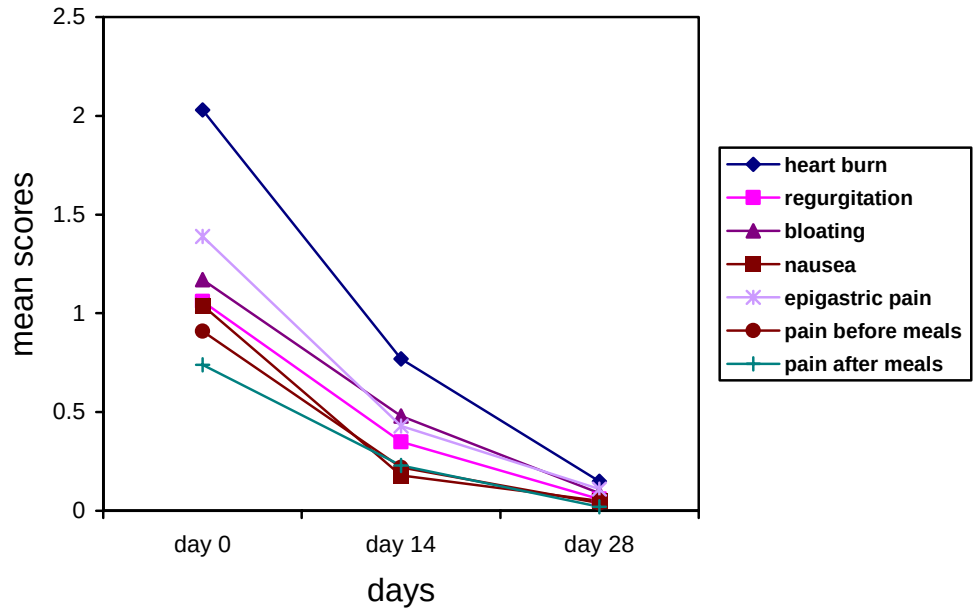
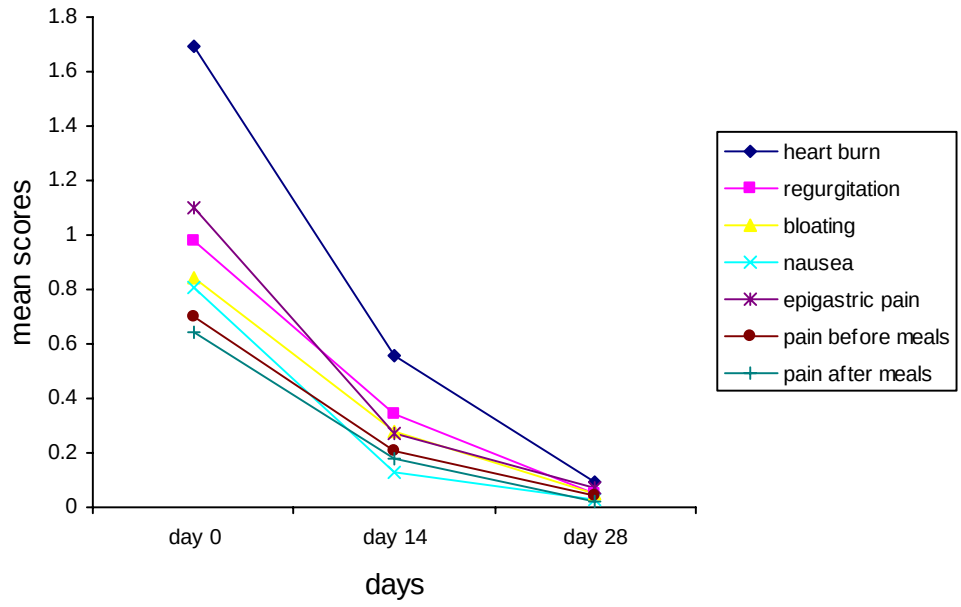


Figure 2: Improvement in mean scores of symptom severity



A significant proportion of patients experienced ≥50% reduction in symptom frequency and severity of heart burn, regurgitation, bloating, nausea, epigastric pain, abdominal pain before meals and in abdominal pain after meals as shown in Table 3.

Table 3: Proportion of patients with ≥50% reduction in symptom frequency* and severity*

Parameter		Day 0, n=	Day 14, n=	Day 28, n=	≥ 50% reduction N; (%), p, (90%CI for %)
Heart burn	**Severity**	0=43 1=49 2= 139 3= 49	0=159 1=91 2=24 3=6	0= 261 1= 15 2= 0 3= 4	N=224 (80%) p<0.0001 (0.7012-0.8675)
	Frequency	0=28 1=33 2=121 3=98	0=114 1=122 2=39 3= 5	0= 247 1= 27 2= 2 3= 4	N=234 (83.57%) P<0.0001 (0.6995-0.8652)
Regurgitation	**Severity**	0= 119 1= 86 2= 37 3= 38	0= 209 1= 52 2= 14 3= 5	0= 269 1= 7 2= 4 3= 0	N=152 (54.29%) p<0.0001 (0.5396-0.7191)
	Frequency	0= 112 1= 82 2= 42 3= 44	0= 204 1= 55 2= 21 3= 0	0= 267 1= 8 2= 5 3= 0	N=158 (56.43%) p<0.0001 (0.5441-0.7212)
Bloating	**Severity**	0= 134 1= 69 2= 66 3= 11	0= 223 1= 37 2= 19 3= 1	0= 269 1= 8 2= 3 3= 0	N=136 (48.57%) p<0.0001 (0.5052-0.6896)
	Frequency	0= 107 1= 64 2= 64 3= 45	0= 191 1= 44 2= 45 3= 0	0= 257 1= 19 2= 4 3= 0	N=157 (56.07%) p<0.0001 (0.5019-0.6755)
Nausea	**Severity**	0= 127 1= 90 2= 53 3= 10	0= 251 1= 22 2= 7 3= 0	0= 274 1= 4 2= 2 3= 0	N=147 (52.5%) p<0.0001 (0,5537-0.7374)
	Frequency	0= 104 1= 96 2= 44 3= 36	0= 240 1= 30 2= 10 3= 0	0= 270 1= 6 2= 4 3= 0	N=170 (60.71%) p<0.0001 (0.5802-0.7561)
Epigastric pain	**Severity**	0= 89 1= 100 2= 67 3= 24	0= 218 1= 48 2= 14 3= 0	0= 267 1= 8 2= 4 3= 1	N=181 (64.64%) p<0.0001 (0.6002-0.7724)

	Frequency	0= 75 1= 80 2= 67 3= 58	0= 183 1= 75 2= 21 3= 1	0= 254 1= 22 2= 4 3= 0	N=185 (66.07%) p<0.0001 (0.5753-0.7436)
Pain before meal	**Severity**	0= 145 1= 80 2= 49 3= 6	0= 236 1= 29 2= 14 3= 1	0= 271 1= 8 2= 1 3= 0	N=126 (45%) p<0.0001 (0.4942-0.6837)
	Frequency	0= 134 1= 71 2= 42 3= 33	0= 230 1= 39 2= 10 3= 1	0= 270 1= 9 2= 1 3= 0	N=139 (49.64%) p<0.0001 (0.5118-0.6966)
Pain after meal	**Severity**	0= 164 1= 62 2= 45 3= 9	0= 238 1= 34 2= 8 3= 0	0= 274 1= 5 2= 1 3= 0	N=112 (40%) p<0.0001 (0.4760-0.6767)
	Frequency	0= 156 1= 60 2= 46 3= 18	0= 223 1= 49 2= 8 3= 0	0= 275 1= 5 2= 0 3= 0	N=121 (43.21%) p<0.0001 (2.332- 3.025)

**Frequency and severity grading scale: 0=absent/none; 1=occasional; 2=frequent/moderate; 3=very frequent/ severe; 4= very severe.*

Adverse symptoms reported include headache, diarrhoea, abdominal pain, nausea, vomiting, dizziness and pruritus. However, the incidences of reporting of adverse clinical symptoms was much lesser compared to the baseline reported incidences of these symptoms (Table 4) and therefore these symptoms could not be necessarily attributed to S-Pantoprazole.

Table 4: Safety assessment

Symptoms	**Present before therapy**	**Present after therapy**	
	(Day 0), n (%)=	**Day 14, n (%)=**	**Day 28, n (%)=**
Headache	32 (11.43%)	17 (6.07%)	5 (1.79%)
Diarrhoea	7 (2.5%)	7 (2.5%)	2 (0.72%)
Abdominal pain	46 (16.43%)	18 (6.43%)	4 (1.43%)
Flatulence	28 (10%)	16 (5.71%)	1 (0.36%)
Rash	1 (0.36%)	2 (0.71%)	0
Pruritus	5 (1.79%)	4 (1.43%)	4 (1.43%)
Nausea	35 (12.5%)	6 (2.14%)	2 (0.71%)
Vomiting	31 (11.1%)	6 (2.14%)	2 (0.71%)

Dizziness	11 (3.93%)	5 (1.79%)	3 (1.07%)
Insomnia	16 (5.71%)	3 (1.07%)	0
Eructation	15 (5.36%)	3 (1.07%)	1 (0.36%)

Study medication was well tolerated and no patient discontinued therapy for adverse events. The patient's and physician's rating for favorable safety and efficacy of study drug was 96.43% and 96.79% respectively (Table 5).

Table 5: Favorable safety and efficacy rating

	By patient	**By doctor**
Safety	270 (96.43%)	270 (96.43%)
Efficacy	271 (96.79%)	271 (96.79%)

Discussion

Pai et al. conducted a randomized, double-blind, multicentric, parallel group, comparative clinical trial (n=369) of S(-) pantoprazole 20 mg versus racemic pantoprazole 40 mg in patients with GERD. The results of this study showed that there was statistically significant between-group difference in the proportion of patients who showed improvement in acid regurgitation and bloating on day 14 and day 28 of treatment, and heart burn on day 28, with higher proportion in the S(-)pantoprazole treated group than in the racemic pantoprazole treated group. This study concluded S-Pantoprazole to be more effective than the racemate in the treatment of patients with GERD.[3]

An open-label, prospective, non-comparative clinical study of S-Pantoprazole 20 mg once a day was conducted in 224 patients suffering from GERD/gastric ulcer/duodenal ulcer showed that the total symptoms' score (mean ± S.E.M) reduced from 22 ± 0.75 on day 0 to 6.3 ± 0.4 on day 14 ($p<0.001$) with further reduction to 2.5 ± 0.27 ($p<0.001$) on continuing the therapy till 28 days. Percentage of patients achieving improvement in symptoms of heart burn, acid regurgitation, bloating, nausea, dysphagia, pain before meal, pain after meal, epigastric pain and nocturnal pain was 88.3, 80.6, 81.4, 85.1, 81.8, 90.7, 87.7, 83.3, 93.8 on day 14 and 99.5, 97.2, 92.9, 95.2, 94.9, 97.7, 95.9, 96.3, 98 on day 28 of therapy. There was also a statistically significant ($p<0.001$) reduction in total symptom score in 22 patients with predominant nocturnal GERD. This study concluded that S-Pantoprazole 20 mg was an effective, safe and well-tolerated PPI in patients with GERD (with or without predominant nocturnal symptoms) and in patients with GU or DU.[4]

The results of the present study in 280 patients showed that S-pantoprazole achieved a significant reduction in the frequency and severity of heart burn, regurgitation, bloating, nausea, epigastric pain, abdominal pain before meals and abdominal pain after meals with

significant proportion of patients experiencing ≥50% reduction in symptoms' frequency and severity compared to baseline ($p<0.0001$). These finding are in alignment with findings of the studies discussed above. S-Pantoprazole was also found to be very well tolerated as per the patients' and doctors' rating of its safety profile.

In the light of facts mentioned above, it is evident that S-Pantoprazole is an effective PPI in the treatment of patients with GERD and/or peptic ulcers. Further, as S-pantoprazole exhibits consistent pharmacokinetics irrespective of metaboliser status and as it provides better efficacy with equal tolerability compared to racemate,[5] it is desirable to use S-Pantoprazole instead of racemate in the treatment of patients with GERD and/or peptic ulcers.

Conclusion

S-Pantoprazole, at half the racemate dose, is an effective PPI in the treatment of patients with GERD and/or peptic ulcers. It is safe and well-tolerated and can be used as an initial PPI or an alternative PPI to racemic pantoprazole in the management of GERD, duodenal ulcer and gastric ulcer patients.

Acknowledgement

The authors thank following doctors who participated in the SPICE-Study.
Dr.K.Gopalakrishna, Hyderabad; Dr.M.Sathyanarayana, Secunderabad; Dr.G.Satyanarayana, Secunderabad; Dr.S.Kamal Kishore, Hyderabad; Dr.T.Badrinaryan, Hyderabad; Dr.Venugopal Ragi, Hyderabad; Dr.Buchibabu, Hyderabad; Dr.Indirani, Hyderabad; Dr.KSH.Kala Singh, Imphal; Dr.G.Poufullung Kabui, Imphal; Dr.Raushan Kumar, Madhubani; Dr.Ajith Kumar Jha, L.Sarai; Dr.Navin Kumar, Dharbanga; Dr.A.K.Guha, Jamshedpur; Dr.P.C.Verma, Patna; Dr.Narendra Mohan Singh, Patna; Dr.M.K.Jha, Patna; Dr.Mohan Prasad, Patna; Dr.R.A.Saquar, Patna; Dr.Uma Shankar Prasad, Patna; Dr.Ashok Kumar, Patna; Dr.Akash Narayani, Patna; Dr.Ajay Kumar, Patna; Dr.R.P.Singh, Ranchi; Dr.A.K.Das, Ranchi; Dr.A.K.Aditya, Ranchi; Dr. Sunil Kumar, Ranchi; Dr.R.B.Singh, Ranchi; Dr.Sumitra Kumari, Ranchi; Dr.Rekha Kumari, Ranchi; Dr.Sanjay Bhagat, Bero; Dr.Ghanshyam Singh, Chapra; Dr.Ashwin Kumar, Chapra; Dr.A.Q.Ansari, Katihar; Dr.S.Sarkar, Purnea; Dr.Santosh Kumar, Ara; Dr.Pramod S Shah, Nashik; Dr.Mrunalini Kelkar, Nashik; Dr.Bharat R Trivedi, Nashik; Dr.V.P.Dhondge, Nashik; Dr.Vijay Ghatge, Nashik; Dr.Sunil N Jadhav, Ahmednagar; Alhaj Dr. Rizwan Khan, Ahmednagar; Dr.R.R.Satalkar, Ahmednagar; Dr.Rahul D Gadekar, Ahmednagar; Dr.P.S.Jaiswal, Ahmednagar; Dr.Amol Karpe, Sangamner; Dr.Praful Bramhe, Shrirampur; Dr.U.B.Kistiya, Kopargaon; Dr.Amol Pathak, Sangamner; Dr.Amol K, Sangamner; Dr.Shirish Pawar, Chalisgaon; Dr.J.B.Rajput, Jalgaon; Dr.Anil R Mehta, Mumbai; Dr.S.H.Shroff, Mumbai; Dr.Santosh V.Nagare,

Mumbai; Dr.Bharat T Desai, Mumbai; Dr.H.K.Sharda, Mumbai; Dr.Kiran J Desai,Mumbai; Dr.Sameer D Patil, Mumbai; Dr.Prathamesh A Mule, Mumbai; Dr.Abhay A Taware, Mumbai; Dr.Girish M Raut, Mumbai; Dr.B.R.Yadav, Mumbai; Dr.Vinod L Desai, Mumbai; Dr.Iqbal A Lodhia, Mumbai; Dr.Y.H.Shaikh, Mumbai; Dr.A.B.Pathan, Mumbai; Dr.Prakash Kawli, Mumbai; Dr.B.N.Shah, Mumbai; Dr.Jawahar S.Khandeparkar, Mumbai; Dr.D.V.Mambhrey, Mumbai; Dr.Pushpa Mahadeokar, Mumbai; Dr.Nitin Patel, Mumbai; Dr.Manoj B M, Mumbai; Dr.Dinesh K Toprani, Mumbai; Dr.P.D.Shah, Mumbai; Dr.Khurshid Alam Ansari, Mumbai; Dr.M.L.Yadav, Mumbai; Dr.Ashok L Bhanushali, Mumbai; Dr.S.V.Kulkarni, Khopoli; Dr.Bharati Ankush, Vashi; Dr.Chandrashekhar R Shinde, Khopoli; Dr.Vasant B Gajare, Mumbai; Dr.Aftab A Siddiqui, Mumbai; Dr.R.S.Shan, Mumbai; Dr.D.Banerjee, Mumbai; Dr.A.K.Bhattacharya, Mumbai; Dr.Chandra Sekhar Saphui, Mumbai; Dr.S.Mukherjee, Mumbai; Dr.C.B.Ansari, Mumbai; Dr.Javaid Eqbal Haque, Mumbai; Dr.Jayadip Das, Mumbai; Dr.P.K.Bhattacharya, Mumbai; Dr.Ashish Malhotra, Mumbai; Dr.Tapas Kumar S, Mumbai; Dr.Udayan Sanyal, Mumbai; Dr.Alok Patnaik, Bhubaneshwar; Dr.Manan Anand, Amritsar; Dr.Nancy Bilkhu, Vallah

References

1. Poole P. Pantoprazole. Am J Health-Syst Pharm 2001; 58(11): 999-1008.

2. Pai V., Pai N. Recent Developments: Chiral switch in PPI therapy: S (-) Pantoprazole. British Medical Journal, South Asia Edition 2006; 22 (2): 112.

3. Pai VG, Pai NV, Thacker HP, Shinde JK, Mandora VP, Erram SS. Comparative clinical trial of S-pantoprazole versus racemic pantoprazole in the treatment of gastro-esophageal reflux disease. World J Gastroenterol 2006; 12(37): 6017-6020.

4. S-Pantoprazole Study Group, India. Results of an Open-label, Prospective, Non-comparative Study to Assess Safety and Efficacy of S-Pantoprazole in Clinical Practice. Indian Medical Gazette 2006; CXL (6): 285-289.

5. Pai V, Pai N. Recent advances in proton pump inhibitor therapy: S-pantoprazole. Gatroenterology Today 2005; 9 (4): 21-24.