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A Study to Evaluate the Symptomatic Efficacy and Safety of Lafaxid™ (Lafutidine 10mg) in Patients with Acid Peptic Disorders in India

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Authors' contributions

This work was carried out in collaboration between both authors. Author BD designed the study, performed the statistical analysis, reviewed the protocol, and wrote the manuscript for publication. Author DS managed the analyses of the study and the literature searches. Both authors read and approved the final manuscript.

Research Article

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ABSTRACT

Aims: To evaluate the symptomatic efficacy and safety of Lafaxid™ (lafutidine 10 mg) in Indian patients with Acid Peptic disorder (APD).
Study Design: An observational, prospective, uncontrolled, open-label multi-centric study.
Place and Duration of Study: Patients were recruited from 12 cities across India by 61 investigators, between October 2010 and December 2011.
Methodology: We included 1500 patients (973 men, 527 women; age range 15-85 years) with Acid Peptic disorder. Lafutidine (10 mg tablets) was prescribed by the physicians as once daily dose (OD) for 28 days. The efficacy was analysed based on the change in the symptom baseline score on the 100 point Visual Analogue Scale (VAS) for individual symptoms, and the safety was determined based on adverse events reported during the study with the prescribed usage of lafutidine on day 14 and day 28 after start of the treatment.
Results: Lafutidine monotherapy was given to 1378 patients. A very high reduction in the mean VAS score was observed from baseline for individual symptoms, viz. nausea, vomiting, belching, heart burn, epigastric pain, acid regurgitation, abdominal bloating & loss of appetite at the end of the study. The global mean VAS score (a sum of individual

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symptom VAS score) of these patients decreased from 120.34 ± 67.58 to 14.18 ± 26.97 at the end of the study (P < .001). There were 124 APD patients, previously treated but uncontrolled, with acid inhibitors like PPIs, H2RAs etc., also showed a significant reduction (157.42 ± 83.88 to 26.47 ± 46.34) in the VAS score on day 28 (P<.001). During the entire study, adverse events of mild and moderate nature were observed in 0.4% (6 patients) of the total patient population.

Conclusion: The present study demonstrates that therapy with Lafaxid™ is symptomatically effective and well tolerated in patients with APDs.

Keywords: Lafutidine; acid peptic disorders; H2-receptor antagonist (H2RA); gastritis; GERD; ulcer.

1. INTRODUCTION

"Acid peptic disorders" (APD) is a collective term used to include many conditions such as GERD, gastritis, dyspepsia, gastric ulcer, duodenal ulcer, esophageal ulcer, Zollinger Ellison Syndrome and Meckel's diverticular ulcer [1,2]. APDs are the result of distinctive, but overlapping pathogenic mechanisms leading to either excessive acid secretion or diminished mucosal defense [1]. Physiologically, a certain amount of acid is secreted by the gastric cells lining the stomach as a natural mechanism which leads to activation of digestive enzymes like pepsin and help in the digestion and assimilation of proteins in the body. Excessive secretion of this acid and pepsin or a weakened stomach mucosal defense is responsible for damage to the delicate mucosal lining of the stomach, esophagus and duodenum resulting in Acid Peptic Disorders [2]. These disorders owing to their chronicity influence the quality of life and productivity of the afflicted patients [3].

A number of strategies have been designed to control APD including the H2 receptor antagonist (H2RAs), proton pump inhibitors (PPIs), antacids and muscarinic antagonist, focusing primarily on decreasing the acid secretion [4,5,6]. Suppression of acid secretion results in symptomatic relief, but the gastric mucosal damage stills remains untreated and a cause of concern [7].

Lafutidine, a potent second generation H2-receptor antagonist, has been reported to have longer H2 receptor blocking activity [8], increased action on the gastric mucosal defensive capacity [10] and enhancement of mucosal blood flow via capsaicin-sensitive sensory neurons [9] thereby providing gastro protective effects even against necrotizing agents such as nonsteriodal anti-inflammatory drugs [8,9]. The gastro protective action of lafutidine includes increase in mucin biosynthesis via stimulation of nitric oxide production [10,11], increasing the thickness of the surface mucus gel layer [12], and maintaining gastric mucosal blood flow and bicarbonate response [13]. Lafutidine has been found to be effective in subjects with Helicobacter Pylori infections and it induces an increase in intragastric pH [14]. The efficacy of lafutidine has been proven clinically in the management of acid peptic disorders as it balances both the aggressive and the defensive factor [15].

The current study was planned to evaluate real life treatment scenario in terms of symptomatic efficacy and safety of lafutidine in patients suffering from APDs. Therefore, an observational, prospective, uncontrolled, open label, multi-centric study was conducted by Zuventus Healthcare Ltd., through a clinical research organization called Vimta Laboratories limited, to collect data on the use of lafutidine in day to day medical practice in India. The

study was conducted by practicing gastroenterologists and Post graduate physicians with specialization in gastroenterology.

2. MATERIALS AND METHODS

2.1 Study Design

This was an observational, prospective, open-label, multicentric study in 1500 patients with APD. They were recruited from 12 cities (Ahmedabad, Allahabad, Chennai, Delhi, Guntur, Guwahati, Hyderabad, Kolkata, Mumbai, Rajkot, Vijyawada and Vizag) across India by 61 investigators (please refer to acknowledgements). The study was conducted as per the applicable Indian regulatory guidance on conducting clinical trials given in Schedule Y and was approved by independent ethics committee Thus, the study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. No other drug was expected to be prescribed for the management of APD by the prescribing medical practitioners during the conduct of the study. However, if any other drug for the management of APD was prescribed, the same was noted in the concomitant medication section of the case report form (CRF) and such patients were considered for efficacy analysis as a separate subgroup.

The eligibility criteria for the patient to be enrolled in the study included adult patients of either sex who had APD based on the investigator's diagnosis (symptomatic presentation as pain and discomfort by the patients), who were never prescribed lafutidine earlier, who were not likely to be pregnant or lactating patients and who did not have history of hypersensitivity to the study drug. Written informed consent was obtained from all the patients before they were enrolled in the study.

The efficacy and safety assessment was done on day 14 and day 28 after the start of the treatment. The efficacy was analysed based on the change in the symptom baseline score on the Visual Analogue Scale (VAS). The eight symptoms of APD for which VAS scoring was observed were nausea, vomiting, belching, heart burn, epigastric pain, acid regurgitation, abdominal bloating and loss of appetite. Based on the severity of each symptom, they were given a score between 0 to 100 on the VAS scale. The safety and tolerability was analysed based on the adverse events reported during the study with the prescribed usage of lafutidine.

2.1.1 Clinical trial registry of India (CTRI)

This study has been registered with the Clinical Trial Registry of India (Reg No: REF/2012/09/003992).

2.2 Study Medication

Lafaxid^{TM}, (lafutidine 10 mg) marketed by Zuventus Healthcare Ltd. Mumbai India, was prescribed as once daily tablet for 28 days.

2.3 Data Collection and Analysis

The demographic data were collected during study and analysed descriptively by using frequency distribution table. The efficacy data were divided into different subgroups such as

(monotherapy subgroup, indications wise subgroup, symptom wise subgroup and previously treated patients) and analysed by using paired t-test. The level of significance was set at *P=.05.*

3. RESULTS

3.1 Demographics: Study Population

The study was conducted on 1500 patients, with 973(64.87%) males and 527(35.13%) females, aged 15-85 years. The demographic details are given in the Table1. All the patients qualified the eligibility criteria and were successfully enrolled in the study.

Table 1. Demographic data of the study population

Demographics		
Gender	n	1500
Female	n (%)	527 (35.13%)
Male	n (%)	973 (64.87%)
	Mean ± SD	9.71 ± 11.45
Age (Years)	Minimum	15
	Median	38
Previously treated patients	n (%)	124 (8.26%)
Comormid conditions	CNS	16 (1.67%)
	CVS	10 (0.67%)
	Respiratory	8 (0.54%)
	Musculoskeletal	2 (0.14%)
	Others	10 (0.67%)

Lafaxid^{TM} was given as a monotherapy in 1378 patients, while the remaining 122 were concomitantly treated with pantoprazole, rabeprazole, domperidone, glimepride, cintapride, mosapride, itopride, lactulose, isabgul, levosulphiride, drotaverine, ondasetrone, celbupride or other medications for gastrointestinal disorders.

3.2 Efficacy Profile

Interestingly all patients in this study responded to Lafutidine therapy and none of the patients had shown worsening of the symptoms. In the monotherapy group 573 out of 1378 patients were left with no symptoms at the end of 28 days of treatment. The observations in the study were assessed as various subgroups (monotherapy subgroup, indications wise subgroup, symptom wise subgroup and previously treated patients). The results for each subgroup analysis are as follows:

3.2.1 Monotherapy subgroup analysis

The percentage reduction in the Global VAS score (a sum of individual symptom VAS score) for all the patients included in the study (1500) is represented in Fig.1. In the monotherapy subgroup, the mean VAS score decreased from 120.34 ± 67.58 to 44.40 ± 38.55 (Δ=75.94, 95% CI 72.87 - 79.01) on day 14 and 14.18 ± 26.97 (Δ=106.15, 95% CI 102.69 - 109.61) on day

28. The VAS score reduction for various symptoms were found to be statistically significant in both mono and concomitant therapy groups *(P <.001).*

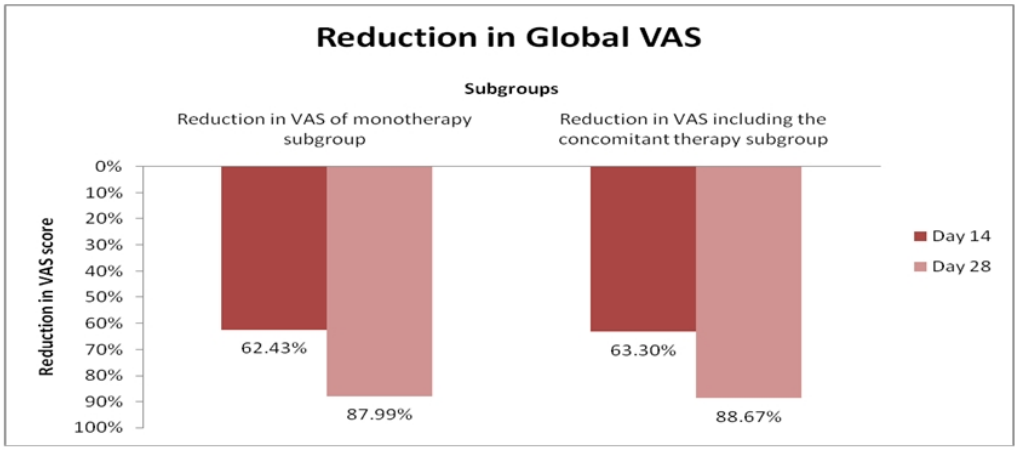

Fig. 1. Percentage reduction in Global VAS score of lafutidine monotherapy subgroup (n=1378) and including the concomitant therapy subgroup (n=1500)

3.2.2 Indication wise subgroup analysis

In the monotherapy subgroup of patients, common indications reported were Dyspepsia (35.5%), Gastritis (38.09%), GERD (24.89%) and Ulcer (0.79%). The mean global VAS score of individual indication is represented in Table 2. Patients having gastritis showed 93.34 % reduction in the VAS score on day 28 *(P <.001*). There was a significant reduction in the VAS score of ulcer patients by 98.9% at the end of the study. *(P< .001)*.

Table 2. Mean VAS score of individual indication at different time points (n=1378)

Indication	Day 0 Mean (% reduction from baseline)	Day 14	Day 28	Mean Difference between Day 0 and Day 28 (95% CI)	P value
Dyspepsia (n=489)	125 ± 62.97	55.22 ± 44.25* (55.7%)	22.09 ± 31.75* (82.3%)	102.91 (97.85 to 107.96)	<.001
GERD (n=343)	119.11 ± 62.18	43.41 ± 34.88* (63.46%)	12.78 ± 21.18* (89.24%)	106.33 (99.66 to 113.00)	<.001
Gastritis (n=525)	116.87 ± 73.71	35.41 ± 32.85* (69.7%)	7.78 ± 22.16* (93.34%)	109.09 (102.82 to 115.35)	<.001
Ulcer (n=11)	175.90 ± 73.71	33.18 ± 17.92* (81.13%)	1.81 ± 3.37* (98.9%)	174.09 (124.73 to 223.45)	<.001

** P Vs baseline*

3.2.3 Symptom wise subgroup analysis

The mean VAS score for nausea, vomiting, belching, heart burn, epigastric pain, acid regurgitation, abdominal bloating & loss of appetite were evaluated and found to be reduced as compared to the baseline values with statistically significant difference (P<.05) as shown in the Table 3.

Table 3. Mean VAS score of individual symptoms of Acid Peptic Disorders at different time points (n=1378)

Sr. No.	Sym ptoms	Day 0	Day 14	Day 28	Mean Difference between Day 0 and Day 28 (95% CI)	P value
		Mean (% reduction from baseline)				
1.	Nausea (n=647)	29.66 ± 15.51	9.93 ± 9.3* (66.5%)	2.9 ± 7.29* (90.08%)	26.77 (25.62 to 27.91)	<.05
2.	Vomiting (n=361)	23.24 ± 14.38	6.87 ± 5.17* (70.43%)	0.97 ± 2.1* (95.82%)	22.28 (20.83 to 23.73)	<.05
3.	Belching (n=734)	30.02 ± 15.30	11.8 ± 10.5* (60.49%)	3.7 ± 6.2* (87.40%)	26.27 (25.29 to 27.26)	<.05
4.	Heart Burn (n=784)	35.29 ± 17.12	13.6 ± 12.02* (61.37%)	5.2 ± 7.7* (85.23%)	30.13 (28.75 to 31.51)	<.05
5.	Epigastric Pain (n=665)	34.91 ± 19.12	14.6 ± 12.3* (58.14%)	6.03 ± 7.5* (82.72%)	28.89 (27.26 to 30.51)	<.05
6.	Acid Regurgitation (n=568)	35.73 ±18.91	13.08 ± 13.7* (63.39%)	4.59 ± 9.3* (87.15%)	31.18 (29.64 to 32.73)	<.05
7.	Abdominal Bloating (n=635)	34.17 ± 16.42	13.2 ± 12.47* (61.48%)	4.47 ± 9.1* (86.91%)	29.81 (28.56 to 31.06)	<.05
8.	Loss of Appetite (n=737)	31.36 ± 17.94	9.9 ± 9.16* (68.41%)	1.32 ± 4.8* (95.82%)	30.39 (29.11 to 31.67)	<.05

** P Vs baseline*

3.2.4 Previously treated subgroup analysis

There were 124 patients who had history of uncontrolled symptoms with earlier treatment for APD which included drugs like PPI (92 patients), first generation H2 receptor antagonist (18 patients), antacid (4 patients), Sucralfate (1 patient) and other miscellaneous drugs and their combinations (9 patients) i.e. PPI with prokinetics, PPI with H2 Antagonist, PPI with Domperidone, PPI with Digestive enzymes. All the patients in this subgroup had a significant reduction in the VAS score (Fig. 2) from 157.42 ± 83.88 to 26.47 ± 46.34 (Δ 130.95, 95% CI 114.00 - 147.90) at the end of treatment period *(P <.001)*. Moreover 55 patients out of 124 previously treated subgroup of patients were symptom free at the end of 28 days of treatment.

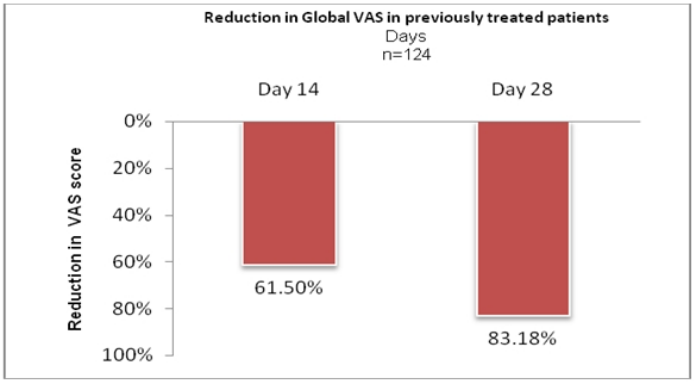

Fig. 2. Percentage reduction in VAS scores of previously treated patients (n=124)

3.3 Safety Profile

There were 9 adverse events reported in 6 patients (0.4%) who were maintained on monotherapy with lafutidine. Out of the 9 adverse events, the severity was reported to be mild for 6 and moderate for 3 events. All the events were resolved without sequelae (Table 4).

Table 4. Summary of adverse events during therapy with lafutidine

Body system	Adverse events	No. (%) of events(n=6)
Gastrointestinal disorders	Abdominal pain	1 (0.072%)
	Diarrhoea	2 (0.145%)
	Belching	1 (0.072%)
	Vomiting	1 (0.072%)
General disorders	Malaise	1 (0.072%)
Nervous system disorders	Excessive Sleep	1 (0.072%)
	Headache	1 (0.072%)
	Fever	1 (0.072%)

4. DISCUSSION

Second-generation H2-blockers are reported to be effective in prevention of APD through the activation of mucosal defense mechanisms [17]. Lafutidine, a second generation H2-blocker, has been shown to enhance the healing of gastrointestinal mucosal lesions in a manner independent of its antisecretory action [9,16]. It was also proven to be more effective than first generation H2RA (famotidine) for acid control during the daytime [27]. In subjects without Helicobacter Pylori infections, evidences have proven that lafutidine noticeably elevates the day time as well as the nocturnal intragastric pH. However, first generation H2RAs elevate only nocturnal intragastric pH [20].

Previously, lafutidine has been elaborately studied and has proven its efficacy in various indications like gastritis, reflux esophagitis, gastric and peptic ulcer, dyspepsia, burning mouth syndrome, glossodynia, as a pre-anesthetic medication and in GERD [18-22]. Results of these studies showed that there was 93% improvement in cases of gastric ulcer, 96.8% in duodenal ulcer and 88.4% in acute and chronic gastritis [23]. In the present study, lafutidine was prescribed for dyspepsia, gastritis, GERD or ulcers and was found to be symptomatically effective in each of the indication as there was 82.3%, 93.34%, 89.24% and 98.90% reduction in the mean VAS score respectively *(P <.001).*

Several clinical trials have proven the superiority of PPIs over first generation H2RA, because the former exert stronger and longer acid suppression than the latter [24,25,26]. Meta analysis evaluating the efficacy of lafutidine over PPI has shown that lafutidine is non inferior [18,19,20,28]. Our study demonstrates that lafutidine was effective in treating patients who were uncontrolled with PPI as there was a 81.74% reduction in the mean VAS score at the end of the study. These observed properties of lafutidine may be attributed to its dual mechanism of action.

Yamagishi et al. reported that lafutidine 10mg has a prompter onset of action than lansoprazole 30mg in the early phase (1-6h) after administration of a single oral dose [18]. This is because all PPIs are enteric coated and absorbed in the small intestine with a delay

of almost 1-2 hours and transported via the systemic circulation to gastric parietal cells [29]. They require some time to accumulate in parietal cells and inhibit acid secretion. H2RAs are absorbed in the small intestine and then they reach gastric cells via the systemic circulation where they directly and rapidly bind to gastric cell histamine receptors causing instant inhibition of gastric acid secretion [18].

In the Literature review of published clinical trials, the most commonly reported adverse events were constipation and changes in biochemistry values in the laboratory tests. It has also been reported that clinically significant adverse reactions such as Shock, anaphylactic reactions, hepatic function disorder, agranulocytosis, thrombocytopenia etc., may occur with its use [19,20,22,23,28]. However, Lafutidine was well tolerated in all the patients enrolled in this study as there was no serious adverse event reported. Adverse events of mild and moderate nature were observed in only 0.4 % of the total patient population. All the adverse events were resolved without sequelae during the study period. The current study has certain limitations in terms of lack of control arm, short duration of treatment period and the inherent weakness of VAS scale which makes the observations subjective. The patients were diagnosed of having APD based on previous history and the Physician's opinion and diagnostic endoscopy was not performed for the confirmation of APD, there might be chances of misdiagnosis as certain patients having gastric cancer could also be enrolled. Since there was no accounting for placebo effect, that could have affected the treatment outcome, it is prudent to consider some patients might have shown improvement by virtue of the placebo effect also. Despite above limitations, this study represents a very practical scenario of patients' treatment from a wide number of centers across India and gives a vivid picture of empirical therapy using Lafutidine in the management of APD. Future studies would be needed to overcome these limitations and to compare its efficacy with other acid suppressive medication.

5. CONCLUSION

The results of the present study conclude that Lafaxid™ (lafutidine 10mg) is safe and symptomatically effective in the management of patients with APD. It is also effective in APD patients uncontrolled on PPIs or first generation H2RAs. Lafutidine can be used as an empiric therapy to treat Acid Peptic Disorders however, further controlled clinical trials on the same are recommended.

CONSENT

Not applicable.

ETHICAL APPROVAL

All authors hereby declare that the trial has been examined and approved by the independent ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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COMPETING INTERESTS

Authors are employed at Zuventus Healthcare Limited.

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