Evaluation of Efficacy and Safety of Gaseex Syrup in Functional Dyspepsia

MG Shekar Kumar*, SR Prasad**, SK Mitra†

*Laparoscopic Surgeon and Consultant Urologist, Shree Sai Hospitals, Choolaimedu, Chennai, India.
**Medical Advisor,
†Executive Director, R&D Center, The Himalaya Drug Company, Bangalore, India.
Address for correspondence:
Dr SR Prasad, R&D Center, The Himalaya Drug Company, Bangalore.
Email: dr.prasad@himalayahealthcare.com

A significant reduction in the mean symptoms score of upper abdominal pain, heartburn, abdominal bloating, belching and fullness of stomach after meals were observed after 28 days of treatment with Gaseex syrup.

Abstract

The present study was planned to evaluate the clinical efficacy and safety of Gaseex syrup in functional dyspepsia. Dyspepsia is a symptom complex of epigastric pain or discomfort believed to originate in the upper gastrointestinal (GI) tract. The pathogenesis of functional dyspepsia remains uncertain. However, symptomatic improvement of patients with functional dyspepsia with current drug therapy is left with many unmet needs. This is because functional dyspepsia is a heterogeneous disease and a uniform response to drug treatment can therefore not be achieved.

The present study was an open clinical trial, conducted as per the ethical guidelines of Declaration of Helsinki. All patients suffering from pain or discomfort centered in the upper abdomen with associated bloating, belching, vomiting and heartburn were included in the study and patients having severe vomiting and diarrhea, and those suffering with gastric or duodenal ulcer, cancer or varices disease were excluded from the study. A thorough history, symptomatic evaluation and clinical examination was done for all patients before treatment and during follow-up visits every week till the end of treatment on day 28 along with recording the occurrence of any adverse event/s. The predefined primary end-points were rapid symptomatic relief from upper abdominal pain, heartburn and bloating. The predefined secondary end-points were short- and long-term safety, and overall compliance to the drug treatment.

A total of 25 patients were enrolled for the trial and all patients completed the study. A significant reduction (p < 0.0001) in the mean symptoms score of upper abdominal pain, heartburn, abdominal bloating, belching and fullness of stomach after meals were observed after 28 days of treatment with Gaseex syrup. There were no clinically significant adverse events, either reported or observed, during the entire study period. Therefore, it may be concluded that Gaseex syrup is clinically safe and effective in the management of functional dyspepsia.

Introduction

Functional dyspepsia is defined as persistent or recurrent abdominal pain or abdominal discomfort centered in the upper abdomen which cannot be explained by structural or biological abnormalities1,2.

Discomfort refers to unpleasant sensations that the subject does not interpret as pain and may be
characterized by upper abdominal fullness, early satiety, bloating, belching or nausea. It is estimated that the annual prevalence of recurrent upper abdominal discomfort in the United States and other Western countries is approximately 25%; about 2-5% of all primary care consultations are related to dyspeptic symptoms. For many patients, the symptoms are of short duration or mild severity. Functional dyspepsia is a highly prevalent symptom complex and a heterogeneous disorder. Recent studies showed potential associations between specific pathophysiologic disturbances and dyspeptic symptoms. Delayed gastric emptying reported in about 30% of patients with functional dyspepsia is associated with symptoms of postprandial fullness, nausea and vomiting. Impaired gastric accommodation present in 40% of functional dyspepsia patients is found to be associated with early satiety. Hypersensitivity to gastric distension is observed in 37% of functional dyspepsia patients and is associated with symptoms of postprandial pain, belching and weight loss. Psychosocial factors and altered response to duodenal lipids or acid have also been identified as pathophysiologic mechanisms. Therapeutic options are still limited but targeted therapy directed at the underlying pathophysiology seems desirable. Symptomatic improvement of patients with functional dyspepsia with current drug therapy is left with many unmet needs. This is because functional dyspepsia is a heterogeneous disease and a uniform response to drug treatment can therefore not be achieved.

Pharmacological treatment for patients with functional dyspepsia remains unsatisfactory.

Gasex syrup is a polyherbal formulation containing extracts of Cuminum cyminum, Mentha arvensis, Foeniculum vulgare, Elettaria cardamomum, Apium graveolens, Coriandrum sativum, Curcuma longa and Trikatu, all of which are recommended for the management of dyspepsia. This study was planned to evaluate the clinical efficacy and safety of Gasex syrup in the management of functional dyspepsia.

Patients and methods

Inclusion criteria

All patients aged between 18 - 55 years, suffering from pain centered in the upper abdomen with associated bloating, heartburn, belching and vomiting were included in the study.

Exclusion criteria

Patients having severe vomiting and diarrhea, irritable bowel syndrome, diabetes mellitus, those suffering with gastric or duodenal ulcer, cancer or variceal disease; and patients with history of gastric surgery or NSAIDs intake were excluded from the study.

Study procedure

The study was an open, non-randomized and non-comparative, prospective, phase III clinical trial, conducted at Shree Sai Hospitals, Choolaimedu, Chennai, India from January 2007 to March 2007, as per the ethical guidelines of Declaration of Helsinki. The study protocol, case report forms (CRFs), regulatory clearance documents, product-related information, and informed consent forms (in English, Hindi and Tamil) were submitted to the institutional ethics committee and were approved by the same.

The patients who attended the OPD general surgical unit of Shree Sai Hospitals, Choolaimedu, Chennai, India were informed about the study drug, its effects, duration of the trial, and overall plan of the study. The patients were included in the clinical study only after written informed consent was obtained from them, and a witness, independent of the clinical trial, signed the informed consent form.

The history was noted by interviewing the patient. Thorough clinical examination and symptomatic evaluation was carried out and the details were noted down in the CRF. Patients were advised to take the drug at a dose of 2 teaspoonfuls twice a day after meals for 28 days.

All patients were followed-up every week till the end of treatment on day 28 and symptomatic evaluation and clinical examination was done, along with recording the occurrence of any adverse event/s (either reported or observed).

Primary and secondary end-points

The predefined primary end-points were rapid symptomatic relief from upper abdominal pain, heartburn, bloating and fullness after meals. The predefined secondary end-points were short- and long-term safety, and overall compliance to the drug treatment.

Adverse events

All adverse events, either reported or observed, were recorded in the CRF with information about severity, onset, duration...
Clinical study and action taken regarding the study drug. Relation of adverse events to the study medication was predefined as “unrelated” (a reaction that does not follow a reasonable temporal sequence from the time of administration of the drug), “possible” (follows a known response pattern to the suspected drug, but could have been produced by the patient’s clinical state or other modes of therapy administered to the patient) and “probable” (follows a known response pattern to the suspected drug that could not be reasonably explained by the known characteristics of the patient’s clinical state).

Patients were allowed to voluntarily withdraw from the study, if they experienced serious discomfort during the study or sustained serious clinical events requiring specific treatment. For patients withdrawing from the study, efforts were made to ascertain the reason for dropout. Non-compliance (defined as failure to take < 80% of the medication) was not regarded as treatment failure, and reasons for non-compliance were noted.

Table 1: Reduction in Mean Symptom Score of Upper Abdominal Pain, Heartburn, Bloating, Belching, and Fullness after Meals with Gasex Syrup Treatment

<table>
<thead>
<tr>
<th>Parameter (symptom score)</th>
<th>Day 0</th>
<th>Day 7</th>
<th>Day 14</th>
<th>Day 21</th>
<th>Day 28</th>
<th>Friedman statistic (FS) and significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper abdominal pain</td>
<td>1.960 ± 0.1869</td>
<td>1.480 ± 0.1645</td>
<td>0.960 ± 0.1222</td>
<td>0.8400 ± 0.1108</td>
<td>0.8000 ± 0.1155</td>
<td>FS: 68.84; p &lt; 0.0001, significant</td>
</tr>
<tr>
<td>Heartburn</td>
<td>0.8800 ± 0.2026</td>
<td>0.7200 ± 0.1583</td>
<td>0.2000 ± 0.0817</td>
<td>0.1200 ± 0.0663</td>
<td>0.0800 ± 0.0554</td>
<td>FS: 49.46; p &lt; 0.0001, significant</td>
</tr>
<tr>
<td>Bloating</td>
<td>1.640 ± 0.1904</td>
<td>1.440 ± 0.1536</td>
<td>1.000 ± 0.1633</td>
<td>0.7600 ± 0.1194</td>
<td>0.6400 ± 0.1275</td>
<td>FS: 57.52; p &lt; 0.0001, significant</td>
</tr>
<tr>
<td>Belching</td>
<td>0.8400 ± 0.1600</td>
<td>0.6800 ± 0.1381</td>
<td>0.2400 ± 0.0872</td>
<td>0.1600 ± 0.0748</td>
<td>0.1600 ± 0.0748</td>
<td>FS: 55.45; p &lt; 0.0001, significant</td>
</tr>
<tr>
<td>Fullness after meals</td>
<td>1.560 ± 0.1833</td>
<td>1.320 ± 0.1497</td>
<td>0.6800 ± 0.1381</td>
<td>0.6000 ± 0.1291</td>
<td>0.5600 ± 0.1013</td>
<td>FS: 61.90; p &lt; 0.0001, significant</td>
</tr>
</tbody>
</table>

The changes in various parameters from pretreatment values to posttreatment values were analyzed by “Friedman’s test” followed by “Dunn’s Multiple Comparison test analysis”. The minimum level of significance was fixed at 95% confidence limit and a two-sided p value of <0.05 was considered significant.

Results

A total of 25 patients suffering from functional dyspepsia were included in the clinical trial and all patients completed the study. The study group had 15 male and 10 female patients. Mean age of the patients was 37.48 years. Brief
history and clinical examination showed that out of 25 patients, all of them were suffering from upper abdominal pain and 13 patients had heartburn, 21 patients had bloating, 15 patients had belching, 21 patients had fullness after meals, 8 had nausea and one patient had vomiting.

A significant reduction (p < 0.0001) in mean symptoms score of upper abdominal pain, heartburn, abdominal bloating, belching and fullness of stomach after meals, were observed after 28 days of treatment with Gasex syrup. The reduction in these symptoms started appearing on the 7th day of treatment itself (Table 1; Fig. 1 - 5).

Nausea and vomiting was present only in eight patients and one patient, respectively and was completely relieved by day 7 itself.

Patient’s global assessment revealed that 24% showed marked improvement, 44% had moderate improvement and 32% had slight improvement after 28 days of therapy with Gasex syrup (Fig. 6).

Investigator’s global assessment revealed that 28% of patients had marked improvement, 56% of them had moderate and 16% of them had slight improvement at the end of treatment with Gasex syrup (Fig. 7).

There were no clinically significant adverse events, either reported or observed, during the entire study period.

Discussion

Functional dyspepsia is a common chronic disorder with non-specific upper abdominal symptoms which cannot be explained by organic or biochemical abnormalities. Functional dyspepsia is far more common than dyspepsia due to organic disease, both in the community and general practice. The dyspeptic symptoms are very compromising and bothersome and result in a substantial reduction of quality-of-life. The substantial direct and indirect medical and economical costs induce a high socioeconomic interest in the pathogenesis and the treatment options of this disease.

Unlike peptic ulcer disease, where treatment is pharmacological and usually straightforward, the management of non-ulcer dyspepsia (as with all functional GI disorders) is more challenging and requires a careful dialogue between
Clinical study

Physician and patient. Underlying pathophysiological disturbances are not fully understood, but include impaired gastric accommodation (upto 40% of patients), delayed gastric emptying (25-40%) and visceral hypersensitivity (33%). Pharmacological treatments are often disappointing and a significant placebo response (20–60%) is usually seen as in other functional GI disorders. Most experts advocate a trial of proton pump inhibitor and/or Helicobacter pylori eradication, if present.

Other treatments include prokinetic drugs (mainly cisapride, subsequently withdrawn in many countries) and these may benefit some. There are also limited data suggesting benefit from bismuth, misoprostol, sucralfate, pirenzepine (antimuscarinic) and antidepressants. Psychological studies have been performed using psychotherapy, cognitive therapy and hypnotherapy with reported improvements in dyspepsia scores.

The present clinical study observed a significant relief in the symptoms of dyspepsia like upper abdominal pain, heartburn, abdominal bloating, abdominal belching, fullness of stomach after meals, nausea and vomiting after 28 days of treatment with Gasex syrup. The reduction in these symptoms started appearing on 7th day of treatment itself and complete relief was observed by 28 days. There were no clinically significant adverse events, either reported or observed, during the entire study period.

Earlier research works on the extracts of individual ingredients of Cuminum cuminum, Mentha arvensis, Foeniculum vulgare, Elettaria cardamomum, Apium graveolens, Coriandrum sativum, Curcuma longa, and Trikatu were credited for their carminative, antispasmodic, analgesic, anti-inflammatory and antioxidant activities.

Cuminum cuminum, belonging to the family Apiaceae, is widely used in Ayurvedic medicine for the treatment of dyspepsia, diarrhea and jaundice. All the herbs tested increased acid secretion in the following declining order: Fennel, omum, cardamom, cumin, coriander. These herbs increased gastric acid secretion, in some by a cholinergic mechanism but by other mechanism(s) as well. Cumin may protect the colon by decreasing the activity of β-glucuronidase and mucinase.

“Trikatu” is an Ayurvedic preparation containing black pepper, long pepper and ginger, which is prescribed routinely for a variety of diseases as part of multidrug prescriptions. These herbs along with piperine (alkaloid of peppers) have been shown to possess diverse biological activities in mammalian systems.

Peppers and ginger have been commonly used in conjunction in folklore medicines. Modern research, mostly European, has documented the ability of ginger to stimulate gastric motility (efficiency of moving food through the digestive tract), to relieve indigestions, and to promote digestion. The main reason that this herbal trio is part of so many Ayurvedic formulations is its proven ability to enhance GI absorption of nutrients. Many groups of scientific investigators attribute this bioenhancing property of pepper to its main alkaloid, piperine.

Mentha arvensis plant has antispasmodic, carminative, cholagogic and antimicrobial properties. The oil contains 95% of menthol and offers cytotoxic properties. The fruit of Foeniculum vulgare has anti-inflammatory, analgesic and antioxidant activities. Elettaria cardamomum has shown gastroprotective property in rats. Extract of Apium graveolens contains apiin as the major constituent and exerted significant anti-inflammatory property in vivo model. The antioxidant activity of the aqueous extracts of three umbelliferous fruits - coriander (Coriandrum sativum), cumin (Cuminum cuminum) and fennel (Foeniculum vulgare) has been demonstrated.

Curcuma longa has been commonly used as a traditional remedy for a variety of symptoms such as inflammation, gastritis and gastric ulcer. When Curcuma longa extract was administered per os to pylori-ligated rat
stomachs, it reduced gastric acid secretion and protected against the formation of gastric mucosal lesions. Therefore, it was tested whether *Curcuma longa* extract inhibits gastric ulcers by blocking the H₂ histamine receptor. These findings suggest that the extract from *Curcuma longa* specifically inhibits gastric acid secretion by blocking H₂ histamine receptors in a competitive manner.17

Therefore, the observed clinical benefits of Gasex syrup might be due to the synergistic actions of its ingredients.

**Conclusion**

Functional dyspepsia is a commonly encountered syndrome in medical practice. Being a multifactorial syndrome complex, many therapeutic interventions have been studied. However, there is no clinically effective and safe medication that can be recommended in the management of functional dyspepsia. This study was conducted to evaluate the clinical efficacy and safety of Gasex syrup in functional dyspepsia.

This study observed a significant symptomatic relief from upper abdominal pain, heartburn, abdominal bloating, belching and fullness of stomach after meals. Symptomatic relief was evident in 14 days of study in majority of the patients, while almost all were relieved within 28 days of treatment. There were no clinically significant adverse events, either reported or observed, during the entire study period. Therefore, it may be concluded that Gasex syrup is clinically safe and effective in the management of functional dyspepsia.

**REFERENCES**