Research Article

The Comparative Study of the Effectiveness of Cimetidine, Ranitidine, Famotidine, and Omeprazole in Treatment of Children with Dyspepsia

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Background. Functional dyspepsia is a common chronic disorder with non-specific upper abdominal pain or discomfort. Different approaches with anti-secretory, spasmolytic, prokinetic and anti-inflammatory effects and most preferably reduction of visceral hypersensitivity seem logical. In this study, we compared the effectiveness of the four most drugs used for treatment of dyspepsia in children.

Methods. 169 patients between 2 to 16 years old that 47.3% was male and 52.7% was female were enrolled in this clinical trial study by the diagnosis of functional dyspepsia. Then for each patient one of the drugs; Omeprazole, Famotidine, Ranitidine or Cimetidine was administered, for a period of 4 weeks. Patients were followed after 2 and 6 weeks from the beginning of the treatment.

Results. The distribution of drugs between these patients were including; 21.9% with Cimetidine, 21.3% with Famotidine, 30.8% with Omeprazole and 26% with Ranitidine that the proportion of patients with all symptoms relief were: 21.6% for Cimetidine, 44.4% for Famotidine, 53.8% for Omeprazole and 43.2% for Cimetidine ($P = 0.024$). In followups within 2 and 6 weeks after beginning medical therapy, no side effects due to drugs were seen.

Conclusion. If a cure is defined as all symptoms relief after a period of 4 weeks treatment, our findings showed that Omeperazole are superior to Ranitidine, Famotidine, and Cimetidine for management of functional dyspepsia.

1. Introduction

Functional dyspepsia (FD) is a very common cause of upper gastrointestinal symptoms and discomfort [1]. FD has been defined as a functional gastrointestinal disorder (FGID) characterized by persistent or recurrent pain or discomfort centered in the upper abdomen that is not relieved by defecation or associated with changes in stool characteristics occurring at least once a week for at least 2 months in the absence of organic diseases [2]. A diagnosis of FD can be made in children mature enough to provide an accurate history of pain that is present for at least a 12-week duration, which need not be consecutive, in the preceding 12 months, the recurrent discomfort is typically centered in the upper abdomen (above the umbilicus), and there is no evidence of organic disease (including at upper endoscopy). In addition, there is no evidence that dyspepsia is exclusively relieved by defecation or is associated with the onset of a change in stool frequency or stool form. There are two presentations of functional dyspepsia, which are ulcer-like dyspepsia and dysmotility-like dyspepsia.

The low prevalence of organic disease found in dyspepsia supports the use of reassurance and empiric therapy as initial treatment, so the Rome committee recommends that an upper gastrointestinal endoscopy should be performed in the presence of dysphagia, persistence of symptoms despite the use of acid reducing medications, or patients with recurrent symptoms after discontinuing such medications [2]. Thus, different approaches with antisecretory, spasmolytic, prokinetic, and anti-inflammatory effects, and,
most preferably, reduction of visceral hypersensitivity seem logical. This could explain the variety of drugs which show a positive symptomatic response [1], currently there is no FDA-approved drug for treatment of FD [3].

Despite the scant evidence, anti-secretory agents are frequently recommended in the treatment of patients with a predominant complaint of pain while prokinetic agents are frequently used for bloating and early satiety [4]. Patients’ symptoms that are severe enough to disrupt daily activities will likely benefit from pharmacologic therapy. Such therapy should be individualized and directed toward the predominant symptom [5].

For patients with predominant dyspepsia (discomfort centered in the epigastrium, nausea, early satiety, postprandial fullness, recurrent emesis), a short course of empiric therapy with an H2-histamine receptor antagonists or proton pump inhibitors is acceptable. There are currently no pediatric data to support the long-term benefit of anti-secretory therapy in patients with FGIDs [5].

The aim of this study is to compare the effectiveness of the commonly four most used drugs for treatment of dyspepsia in children, including Omeprazole, Ranitidine, Cimetidine, and Famotidine in a period of 4 weeks of treatment.

2. Patients and Methods

In this clinical trial study, 169 children between 2 and 16 years old were enrolled with the diagnosis of FD which was made by a history of recurrent or persistent abdominal pain and discomfort which was typically centered in the upper abdomen for at least a 12-week duration without any evidence of organic disorder. The other symptoms were early satiety, postprandial abdominal floating or distention, nausea and vomiting. Patients over 18 years old, and whom their medical therapy could not be completed, and those with symptoms including, fever over 38 centigrade degrees, night sweating, weight loss more than 3 kg during past month, frequent vomiting, hematochezia or hematemesis, severe localized pain, and dysphagia, were excluded from this study. Then, for each patient, one of the acid suppressant medications, Omeprazole, Famotidine, Ranitidine, or Cimetidine was administered, for a period of 4 weeks. The under study, 169 children with various dyspeptic symptoms who participated in this study, 80 patients (43.7%) were males and 89 patients (52.7%) were females. The mean age of the patients was 7.4 ± 3.2 years (range, 2–16 years).

The mean duration of the disease among the patients was 15.9 ± 14.2 months (range, 3–60 months), and the mean of their weight was 25.6 ± 11.7 kg (range, 12–60 kg). Ninety-nine patients (58.6%) had a positive family history of FD, and 52 patients (30.8%) were passive smokers. In 108 patients (63.9%), symptoms were related to food consumption; occurrence of the symptoms in 35 patients (32.4%) was before, in 55 patients (50.9%) was after, and in 18 patients (16.7%) was both before and after food consumption. In 61 patients (36.1%), there was no relation between meal consumption and symptoms.

Symptoms distributions are mentioned in Table 1. None of the patients had all the symptoms simultaneously.

Of these 169 children, 37 (21.9%) patients were treated with Cimetidine, 36 (21.3%) with Famotidine, 44 (26%) with Ranitidine, and 52 (30.8%) with Omeprazole. The most common symptoms relieved regardless of type of medication were nausea (86.2%), vomiting (80.8%), and heart burn (79.5%). Abdominal pain was relieved in 63.9%. The distribution and percentage of symptoms being relieved regardless of the specific medication being administered are shown in Table 2.

When different medications were compared, abdominal pain was improved in 45.9%, 65.9%, 66.7%, and 73.1% of Cimetidine, Ranitidine, Famotidine, and Omeprazole groups, respectively, these differences were statistically significant (P < .05). The distribution and percentage of symptoms being relieved in relation to the specific medication used are mentioned in Table 3.

The most influenced symptoms followed by medical therapy in relation with specific medication were chest pain in Famotidine group (100%), vomiting in Ranitidine group (92.7%), nausea and vomiting in Cimetidine group (90%), and nausea in Omeprazole group (87.8%), respectively. The least influenced symptoms followed by medical therapy in relation with specific medication was halitosis in all groups, 25.9%, 44.8%, 51.5%, and 52.5% in Cimetidine, Famotidine, Ranitidine, and Omeprazole groups, respectively.

### Table 1: Distribution of symptoms in all patients.

| Symptom                  | Distribution | Percentage |
|--------------------------|--------------|------------|
| Abdominal pain           | 169          | 100        |
| Halitosis                | 129          | 76.3       |
| Nausea                   | 87           | 51.4       |
| Anorexia                 | 87           | 51.4       |
| Nocturnal awakening      | 76           | 44.9       |
| Early satiety            | 54           | 31.9       |
| Vomiting                 | 47           | 27.8       |
| Heart burn               | 39           | 23.1       |
| Chest pain               | 19           | 11.2       |

3. Results
were relieved, not considering the specific medication being statistically significant (53.8% (28 out of 52) in Omeprazole group, dimin in Ranitidine, 44.4% (16 out of 36) in Famotidine, and this cure rate in other groups were 43.2% (19 out of 44) 37 patients who took Cimetidine cured completely (21.6%), some studies in children have shown peers, and their parents frequently missed work to take care abdominal pain were found to miss more school than their with more than 8 weeks in 24% of them. Children with prevalence of abdominal pain and persistence of symptoms among the most common conditions in children. A school- based study in the United States showed a 38% overall weekly FGIDs, including functional abdominal pain (FAP), are among the most common conditions in children. A school- based study in the United States showed a 38% overall weekly prevalence of abdominal pain and persistence of symptoms for more than 8 weeks in 24% of them. Children with abdominal pain were found to miss more school than their peers, and their parents frequently missed work to take care of their children [6]. Some studies in children have shown an association between chronic or recurrent abdominal pain and higher depression and anxiety scores and poor quality of life [6]. Despite its high frequency and significant impact on quality of life in children, there is only limited evidence to support most treatments that are commonly used to treat childhood FAP. Dietary recommendations may be helpful for some patients with functional recurrent abdominal pain of childhood [7]. There are different medical therapies with different medications for treatment of this disorder in children. In FD, the placebo response has varied form 13–73% [8]. Patients’ symptoms that are severe enough to disrupt daily activities will likely benefit from pharmacologic therapy [8]. Such therapy should be individualized and directed toward the predominant symptom [8]. Treatment modalities include medications, diet modification, herbal preparations, and behaviorally psychologic interventions [9]. Enteric-coated peppermint-oil capsules, believed to exert calcium channel blockade in smooth muscle, were shown in a randomized, placebo-controlled study to decrease the severity of abdominal pain, but not other symptoms in pediatric patients with irritable bowel syndrome [9]. Pharmacotherapy for treatment of FGIDs consists of anticholinergic agents, tricyclic antidepressants, serotonergic agents, selective serotonin reuptake inhibitors, 5-HT3 receptor antagonists, 5-HT4 receptor agonists, and acid suppressive therapy [5]. For patients with predominant dyspepsia (discomfort centered in the epigastrium, nausea, early satiety, postprandial fullness, recurrent emesis), a short course of empiric therapy with H2-receptor antagonists or proton pump inhibitors is acceptable [5]. Some meta-analysis studies showed that H2-receptor antagonists did or did not have a significant therapeutic effect in FD [10, 11]. A meta-analysis of randomized controlled clinical trials has shown that there may be a benefit in the use of H2-receptor antagonists in patients suffering from FD [12]. In another study, it was found that Famotidine was equally effective as placebo [6].

In a meta-analysis, proton pump inhibitors were regarded as superior to H2-receptor antagonists and antacids in patients with “noninvestigated” dyspepsia [13]. H2-receptor antagonists and antacids showed positive effects in approximately 40% of patients (which is in the range of the placebo response rate) whereas proton pump inhibitors response rates were significantly higher, adding an additional 20% [1]. In two preliminary studies of Omeprazole, a proton pump inhibitor, for the treatment of nonulcer dyspepsia, only 50% of the patients treated with Omeprazole had a response, as compared with 25% of those receiving placebo [14]. In a double-blind randomized placebo-controlled study of 4 weeks of Lansoprazole (a proton pump inhibitor) for the treatment of FD in Chinese patients, findings implicated that proton pump inhibitors treatment was not superior to placebo for the management of FD in Chinese patients [15]. Proton pump inhibitors especially improved the symptoms of epigastric pain and heart burn [1]. Several studies in the primary care setting have concluded that proton pump inhibitors are more effective than H2-receptor antagonists or antacids in treating heart burn and dyspeptic symptoms [16]. Therefore, empiric acid suppression would seem to be the favored management approach for the treatment of FD [17].

Since the various proton pump inhibitors are of equivalent efficacy and safety, the cost and acceptability of a particular proton pump inhibitor preparation may be more important when selecting among them than comparable efficacy [18].

### Table 2: Distribution and percentage of symptoms being relieved regardless of the specific medication.

| Symptom           | Distribution before treatment | Symptoms being relieved | Percentage of symptoms being relieved |
|-------------------|-------------------------------|-------------------------|--------------------------------------|
| Nausea            | 87                            | 75                      | 86.2                                 |
| Vomiting          | 47                            | 38                      | 80.8                                 |
| Heart burn        | 39                            | 31                      | 79.5                                 |
| Nocturnal awakening | 76                         | 54                      | 71                                   |
| Chest pain        | 19                            | 13                      | 68.4                                 |
| Early satiety     | 54                            | 35                      | 64.8                                 |
| Abdominal pain    | 169                           | 108                     | 63.9                                 |
| Anorexia          | 87                            | 46                      | 52.9                                 |
| Halitosis         | 129                           | 58                      | 44.9                                 |

In 71 out of 169 patients (42%), all of the symptoms were relieved, not considering the specific medication being taken by them. When different medications compared 8 of 37 patients who took Cimetidine cured completely (21.6%), this cure rate in other groups were 43.2% (19 out of 44) in Ranitidine, 44.4% (16 out of 36) in Famotidine, and 53.8% (28 out of 52) in Omeprazole group, differences were statistically significant (P = .024). In the followups during 2 and 6 weeks after medical therapy, no side effects due to medical therapy were seen.
| Symptoms          | Patients | Drug       | Patients before treatment | Percentage before treatment | Patients whom their symptoms relieved | Percentage of whom their symptoms relieved | P-value* |
|-------------------|----------|------------|---------------------------|-----------------------------|---------------------------------------|------------------------------------------|----------|
| Abdominal pain    | 169      | Cimetidine | 37                        | 21.9                        | 17                                    | 45.9                                     | <.05     |
|                   |          | Famotidine | 36                        | 21.3                        | 24                                    | 66.7                                     |          |
|                   |          | Omeprazole | 52                        | 30.8                        | 38                                    | 73.1                                     |          |
|                   |          | Ranitidine | 44                        | 26                          | 29                                    | 65.9                                     |          |
| Epigastric pain   | 89       | Cimetidine | 21                        | 23.6                        | 6                                     | 28.6                                     | <.05     |
|                   |          | Famotidine | 19                        | 21.3                        | 13                                    | 68.4                                     |          |
|                   |          | Omeprazole | 30                        | 33.7                        | 20                                    | 66.7                                     |          |
|                   |          | Ranitidine | 19                        | 21.3                        | 13                                    | 68.4                                     |          |
| Periumbilical pain| 95       | Cimetidine | 20                        | 21                          | 11                                    | 55                                       | >.05     |
|                   |          | Famotidine | 17                        | 17.9                        | 11                                    | 64                                       |          |
|                   |          | Omeprazole | 31                        | 32.6                        | 23                                    | 74                                       |          |
|                   |          | Ranitidine | 27                        | 28.5                        | 16                                    | 59                                       |          |
| Nausea            | 87       | Cimetidine | 20                        | 23                          | 18                                    | 90                                       | >.05     |
|                   |          | Famotidine | 13                        | 15                          | 11                                    | 84                                       |          |
|                   |          | Omeprazole | 33                        | 38                          | 29                                    | 87.8                                     |          |
|                   |          | Ranitidine | 21                        | 24                          | 17                                    | 80.9                                     |          |
| Vomiting          | 47       | Cimetidine | 10                        | 21.3                        | 9                                     | 90                                       | >.05     |
|                   |          | Famotidine | 8                         | 17                          | 6                                     | 75                                       |          |
|                   |          | Omeprazole | 17                        | 36.2                        | 12                                    | 70.6                                     |          |
|                   |          | Ranitidine | 12                        | 25.5                        | 11                                    | 91.7                                     |          |
| Anorexia          | 87       | Cimetidine | 18                        | 20.7                        | 8                                     | 44.4                                     | >.05     |
|                   |          | Famotidine | 24                        | 27.6                        | 12                                    | 50                                       |          |
|                   |          | Omeprazole | 24                        | 27.6                        | 13                                    | 54.2                                     |          |
|                   |          | Ranitidine | 21                        | 24                          | 13                                    | 61.9                                     |          |
| Early satiety     | 54       | Cimetidine | 15                        | 27.8                        | 10                                    | 66.7                                     | >.05     |
|                   |          | Famotidine | 12                        | 22                          | 6                                     | 50                                       |          |
|                   |          | Omeprazole | 13                        | 24                          | 11                                    | 84.6                                     |          |
|                   |          | Ranitidine | 14                        | 25.6                        | 8                                     | 57.1                                     |          |
| Heart burn        | 39       | Cimetidine | 6                         | 15.4                        | 3                                     | 50                                       | >.05     |
|                   |          | Famotidine | 8                         | 20.5                        | 7                                     | 87.5                                     |          |
|                   |          | Omeprazole | 19                        | 48.7                        | 16                                    | 54.2                                     |          |
|                   |          | Ranitidine | 6                         | 15.4                        | 5                                     | 83.3                                     |          |
| Chest pain        | 19       | Cimetidine | 5                         | 26.3                        | 2                                     | 40                                       | >.05     |
|                   |          | Famotidine | 2                         | 10.5                        | 2                                     | 100                                      |          |
|                   |          | Omeprazole | 8                         | 42                          | 6                                     | 75                                       |          |
|                   |          | Ranitidine | 4                         | 21                          | 3                                     | 75                                       |          |
| Halitosis         | 129      | Cimetidine | 27                        | 21                          | 7                                     | 25.9                                     | >.05     |
|                   |          | Famotidine | 29                        | 22.5                        | 13                                    | 44.8                                     |          |
|                   |          | Omeprazole | 40                        | 31                          | 21                                    | 52.5                                     |          |
|                   |          | Ranitidine | 33                        | 25.6                        | 17                                    | 51.5                                     |          |
| Nocturnal awakening| 76      | Cimetidine | 16                        | 21                          | 9                                     | 56.3                                     | >.05     |
|                   |          | Famotidine | 18                        | 23.7                        | 14                                    | 77.7                                     |          |
|                   |          | Omeprazole | 24                        | 31.6                        | 18                                    | 75                                       |          |
|                   |          | Ranitidine | 18                        | 23.7                        | 13                                    | 72.2                                     |          |

* The P-value is indicative of comparison between various medications effectiveness with each symptom relief.
In this study, we compared the effectiveness of four medications including Cimetidine, Famotidine, Ranitidine (all of them H2-receptor antagonists), and Omeprazole (a proton pump inhibitor), for treatment of children with dyspeptic symptoms, to find the best one for this reason. So if a cure is defined as all symptoms relief after a period of 4 weeks treatment, our analysis indicates that there is a significant difference between response rate and the specific medication being used ($P = 0.024$), and it reveals that the most effective medication, when considering cure as all symptoms being relieved, was Omeprazole with response rate of 53.8% and then with Famotidine (44.4%), Ranitidine (43.2%), and, at last, with Cimetidine (21.6%). Although no significant difference ($P = 0.06$) was found in abdominal pain relief in relation with specific medication consumption, but due to higher response to Omeprazole, it seems that Omeprazole was better than others, and Cimetidine had the least effect. Also, there were no significant differences between other symptoms relief ($P > 0.05$) and the specific medication taken by the patients, except for epigastric pain which responds significantly ($P = 0.018$) to Famotidine and Ranitidine with response rate of 68.4% then Omeprazole with 66.7% and at last Cimetidine with 26.8%.

According to our results and the fact that no significant side effects being detected, and also due to the fact that Ranitidine and Omeprazole were the most effective medications on only one of the symptoms (epigastric pain) comparing with Omeprazole that had the best result on all symptoms being relieved, it cannot be concluded that Ranitidine and Famotidine have equal or better effect in treatment of FD, but, in fact, the best medical therapy for treatment of FD is Omeprazole, or in another way Omeprazole is superior to H2-receptor antagonists for treatment of FD.

At the end it is important to note that since 3 of 4 medications that we used in our study had approximately an equivalent efficacy and safety, the cost of a particular medication may be more important, when selecting among them, than comparable efficacy.

References

[1] H. D. Allescher, “Functional dyspepsia—a multicausal disease and its therapy,” Phytomedicine, vol. 13, no. 1, pp. 2–11, 2006.
[2] A. Rasquin, C. Di Lorenzo, D. Forbes et al., “Childhood functional gastrointestinal disorders: child/adolescent,” Gastroenterology, vol. 130, no. 5, pp. 1527–1537, 2006.
[3] S. Soo, P. Moayyedi, J. Deeks, B. Delaney, M. Lewis, and D. Forman, “Psychological interventions for non-ulcer dyspepsia,” Cochrane Database of Systematic Reviews, Article ID CD002301, 2005.
[4] J. Tack, D. Broeckaert, B. Coulie, and J. Janssens, “The influence of cisapride on gastric tone and the perception of gastric distension,” Alimentary Pharmacology and Therapeutics, vol. 12, no. 8, pp. 761–766, 1998.
[5] A. Lori, L. A. Mahajan, and B. Kaplan, “Chronic abdominal pain of childhood and adolescence,” in Pediatric Gastrointestinal and Liver Disease Pathophysiology/Diagnosis/Management, vol. 7, pp. 112–125, 3rd edition, 2006.
[6] M. Saps and C. Di Lorenzo, “Pharmacotherapy for functional gastrointestinal disorders in children,” Journal of Pediatric Gastroenterology and Nutrition, vol. 48, pp. S101–S103, 2009.
[7] J. S. Hyams, “Chronic abdominal pain caused by sorbitol malabsorption,” Journal of Pediatrics, vol. 100, no. 5, pp. 772–773, 1982.
[8] C. Peck and G. Coleman, “Implications of placebo theory for clinical research and practice in pain management,” Theoretical Medicine, vol. 12, no. 3, pp. 247–270, 1991.
[9] J. S. Hyams, “Treatment of functional gastrointestinal disorders associated with abdominal pain,” Journal of Pediatric Gastroenterology and Nutrition, vol. 41, no. 1, pp. S47–S48, 2005.
[10] G. Dobrilla, M. Comberlato, A. Steele, and P. Vallaperta, “Drug treatment of functional dyspepsia. A meta-analysis of randomized controlled clinical trials,” Journal of Clinical Gastroenterology, vol. 11, no. 2, pp. 169–177, 1989.
[11] H. D. Allescher, A. Böckenhoff, G. Knapp, M. Wienbeck, and J. Hartung, “Treatment of non-ulcer dyspepsia: a meta-analysis of placebo-controlled prospective studies,” Scandinavian Journal of Gastroenterology, vol. 36, no. 9, pp. 934–941, 2001.
[12] H. A. Redstone, N. Barrowman, and S. J. O. van Velthuysen Zanten, “H2-receptor antagonists in the treatment of functional (nonulcer) dyspepsia: a meta-analysis of randomized controlled clinical trials,” Alimentary Pharmacology and Therapeutics, vol. 15, no. 9, pp. 1291–1299, 2001.
[13] B. Delaney, A. C. Ford, D. Forman, P. Moayyedi, and M. Qume, “Initial management strategies for dyspepsia,” Cochrane Database of Systematic Reviews, no. 4, Article ID CD001961, 2005.
[14] R. S. Fisher and H. P. Parkman, “Management of nonulcer dyspepsia,” The New England Journal of Medicine, vol. 339, no. 19, pp. 1376–1381, 1998.
[15] W. M. Wong, B. C. Y. Wong, W. K. Hung et al., “Double blind, randomised, placebo controlled study of four weeks of lansoprazole for the treatment of functional dyspepsia in Chinese patients,” Gut, vol. 51, no. 4, pp. 502–506, 2002.
[16] P. E. Hyman, A. Rasquin-Weber, D. R. Fleisher et al., “Rome II: childhood functional gastrointestinal disorders,” in Rome II: The Functional Gastrointestinal Disorders. Diagnosis, Pathophysiology and Treatment: A multinational Consensus, D. A. Drossman, Ed., pp. 533–575, Allen Press, Lawrence, Kan, USA, 2nd edition, 2000.
[17] D. A. Peura, J. Gudmundson, N. Siepman, B. L. Pilmer, and J. Freston, “Proton pump inhibitors: effective first-line treatment for management of dyspepsia,” Digestive Diseases and Sciences, vol. 52, no. 4, pp. 983–987, 2007.
[18] C. D. Rudolph and E. Hanssal, “Gastroesophageal Reflux,” Walker’s Gastointestinal Disease, vol. 4, no. 2, pp. 66–71, 2008.