International Journal of Family Medicine and Primary Care

Case Report
Published: 01 Dec, 2020

A Unique Case of Gastroparesis *Vs*. Functional Dyspepsia: The Role of Buspirone

Sadiku M[1], Rodriguez C[1] and Veltri KT[1,2]*

[1]*Touro College of Pharmacy, New York, USA*

[2]*Montefiore Medical Center, Bronx, New York, USA*

Abstract

Gastroparesis is a chronic disorder of the stomach characterized by delayed emptying without evidence of mechanical obstruction. Gastroparesis is identified in clinical practice through the recognition of these clinical symptoms and confirmative diagnosis of delayed gastric emptying. Buspirone is the first of a class of selective serotonin-5-HT1A receptor partial agonists indicated for the management of anxiety. It also has some effect on dopamine-D2 autoreceptors and, like antidepressants, can down-regulate β-adrenergic receptors. Newly defined interests in the pathophysiology behind gastroparesis provide promise for a new era of treatment options including buspirone. The rationale for using buspirone in the treatment of gastroparesis and FD is secondary to impaired gastric accommodation.

Keywords: Gastroparesis; Functional dyspepsia; Postprandial distress syndrome; Epigastric pain syndrome

Introduction

Gastroparesis is a chronic disorder of the stomach characterized by delayed emptying without evidence of mechanical obstruction. Hallmark symptoms include nausea, vomiting, early satiety, postprandial fullness, and belching, bloating and upper abdominal pain. Gastroparesis is identified in clinical practice through the recognition of these clinical symptoms and confirmative diagnosis of delayed gastric emptying [1,2]. Certain factors that may increase the risk of gastroparesis include, diabetes, abdominal or esophageal surgery, viral infections, medications that slow the rate of stomach emptying, scleroderma, Parkinson's Disease or Multiple Sclerosis and hypothyroidism. If untreated, gastroparesis can cause several complications, including dehydration, malnutrition and bezoars. Although gastroparesis does not directly cause diabetes, disruptions in the rate and amount of food passing into the small bowel can cause alterations in blood glucose levels. Acute symptom flares could make it difficult for diagnosed individuals to complete routine responsibilities resulting in overall decreased quality of life [3].

If gastroparesis is suspected, a 4 h gastric emptying study is ideally recommended and dietary changes such as a low fat, low fiber diet, and glycemic control among diabetics should be encouraged. Pharmacological treatment options include prokinetics, such as, metoclopramide, domperidone, and erythromycin [1,2]. Treatment with antiemetics should be used for improvement of associated nausea and vomiting. Promethazine, an antihistamine with potent anticholinergic and weak antidopaminergic properties and prochlorperazine a potent antidopaminergic, weak antihistamine, anticholinergic agents are both commonly prescribed as first-line options and have been well studied. Other second line agents include 5-HT3 antagonists and synthetic cannabinoids. The 5-HT3 antagonists, such as ondansetron and granisetron, have shown efficacy, but have not been studied in comparison to older antiemetics for gastroparesis. The synthetic cannabinoid dronabinol has also been used in practice, but there is risk of hyperemesis on withdrawal, and optimum treatment strategies are unclear. Although any of these agents may aid in reducing symptom severity in patients suffering with gastroparesis, they do not treat the underlying cause of altered gastric emptying [1,4].

Gastric accommodation is defined as a vagal nerve mediated reflex associated with reductions in gastric tone along with an increase in gastric volume occurring mainly during meal ingestion. Impaired accommodation is present in approximately 50% of gastroparesis patients and is associated with more prevalent symptoms. No pharmacological treatment of proven efficacy is currently available for patients with impaired gastric accommodation [5]. Therefore, proper assessment of

OPEN ACCESS

Correspondence:
Veltri KT, Touro College of Pharmacy, New York, USA,
E-mail: keith.veltri@touro.edu

Received Date: *03 Nov 2020*
Accepted Date: *25 Nov 2020*
Published Date: *01 Dec 2020*

Citation:
Sadiku M, Rodriguez C, Veltri KT. A Unique Case of Gastroparesis Vs. Functional Dyspepsia: The Role of Buspirone. Int J Fam Med Prim Care. 2020; 1(6): 1026.

Table 1: Glucose laboratory values (fasting).

Glucose Laboratory Values						
11/01	11/02	11/03	11/04	11/05	11/06	11/07
270 mg/dL	227 mg/dL	183 mg/dL	191 mg/dL	148 mg/dL	143 mg/dL	136 mg/dL

gastric accommodation can essentially guide the development of new treatment options. Functional Dyspepsia (FD) can be described as a chronic disorder in the upper digestive tract. For a patient to be diagnosed with FD they must display one or more of the following symptoms: postprandial fullness, early satiation, epigastric pain or burning, and no evidence of structural disease. Most patients with FD have normal gastric emptying; therefore, routine motility testing is not required.

There are two subgroups of FD; Postprandial Distress Syndrome (PDS) and Epigastric Pain Syndrome (EPS). PDS occurs when a patient displays dyspeptic symptoms after eating a meal, whereas EPS is the presence of epigastric pain or a burning sensation in the upper digestive tract. FD can be caused by several abnormalities, including delayed or accelerated impairment of gastric emptying rates and impairment of gastric accommodation. Treatments for FD consist of dietary modifications and pharmacological therapy to target gastric acid secretion and impaired gut motility [6]. The chief treatments for FD target gastric acid secretion and impaired gut motility [6-8]. Patients with EPS benefit more from acid secretion inhibitors.

Classes of acid suppression therapy include H2 receptor antagonist and Proton Pump Inhibitors (PPI). Patients with PDS are advised to take prokinetic agents [6]. However, due to the associated risk of tachyphylaxis, and the adverse events related to these agents, short-term or alternative use of these drugs could be recommended for the symptomatic relief of FD. Other treatments used for FD include serotonin 5-HT3 receptor antagonists and tricyclic antidepressants. Antidepressant therapy is useful for FD associated with normal gastric emptying, but not in FD associated with delayed gastric emptying. Tricyclic antidepressants showed significant effects compared to placebo, but the risk of adverse events outweigh the benefits [6].

Buspirone is the first of a class of selective serotonin-5-HT1A receptor partial agonists indicated functional dyspepsia description as well the management of anxiety. It also has some effect on dopamine-D2 auto receptors and, like antidepressants, can down-regulate β-adrenergic receptors. Its exact anxiolytic mechanism of action is complex and not clearly defined [10]. Previous studies have suggested the involvement of 5-HT1A receptors in the control of gastric tone. In the enteric nervous system activation of 5-HT1A receptors decreases the release of acetylcholine from excitatory motor neurons promoting fundic relaxation and augments gastric accommodation improving postprandial symptoms in patients with FD [9,10]. Although there is significant overlap with gastroparesis and FD, differentiating between the two is important in determining proper treatments. For example, a patient with gastroparesis may be initiated on prokinetics, whereas acid suppression is mainstay therapy for FD.

Occasionally a patient with FD who has persistent symptoms of nausea and vomiting may have a marked delay in gastric emptying potentially leading to a change in therapy. However, data from randomized controlled trials describing this management change is lacking and due to overlapping symptoms, efforts to distinguish FD from gastroparesis by symptoms alone have often failed. Gastroparesis Cardinal Symptoms Index (GCSI) is a questionnaire commonly used in trials. Although it is unclear how relevant gastric emptying measurements relate to FD or gastroparesis, these can assist in guiding patients in receiving the most appropriate therapy. Moreover, although it is unlikely that GCSI questionnaires will help differentiate patients who have FD from patients who have gastroparesis, they have persistently proven to be useful for research studies and analyzing symptom severity in patients [11].

Case Presentation

The following case report describes a patient who was treated with buspirone for persistent nausea and vomiting and epigastric pain.

Our patient is a 58-year-old male with a medical history of hypertension, uncontrolled type II diabetes mellitus and arthritis. Symptoms of nausea and vomiting began in 2012. Esophagogastroduodenoscopy (EGD) revealed gastritis due to H. Pylori which was subsequently treated. The gastric emptying test at the time was within normal limits. The patient exhibited symptoms on and off until he was finally admitted to the Family Medicine Unit of the medical center for postprandial nausea and vomiting on three separate visits in March, September and early October of 2018. The patient's symptoms were originally thought to be due to gastroparesis, however, among several negative results, one study did reveal rapid gastric emptying. EGD was remarkable for mild esophagitis and was treated with famotidine and metoclopramide. On October 13th, 2018, the patient was seen by his primary care physician who prescribed him a 14-day course of metoclopramide and pantoprazole. Resolution of symptoms was short-lived. On November 1st, 2018, the patient presented to the Emergency Department (ED) with intractable nausea and vomiting for the last two days with epigastric pain and weakness. Upon initial treatment during the ED visit, the patient was treated with metoclopramide and famotidine as thought to have gastroparesis. Treatment was followed by Intravenous (IV) fluids and ondansetron for nausea as needed. The patient's vomiting was resolved. He was able to tolerate oral administration and was discharged on ondansetron the same day. The following morning however, the patient returned to the ED with subsequent vomiting episodes. The patient was treated with additional IV ondansetron followed by prochlorperazine. Due to unresolved symptoms, the decision was made to admit the patient.

During his hospital stay, the patient was given fluid repletion and initiated on a clear liquid diet. In addition, the patient was started on metoclopramide 5 mg QID for gastroparesis as it had helped relieve his symptoms in the past. The treatment plan also included ondansetron 4 mg, every eight hours, to control intractable nausea and vomiting, and famotidine 20 mg twice daily for mild esophagitis. Although his symptoms improved during his hospital stay, the

Table 2: Blood Pressure Readings (Daily Average).

Blood Pressure Readings						
11/01	11/02	11/03	11/04	11/05	11/06	11/07
155/80	160/75	145 /93	144/93	148/94	125/68	129/71

physician suspected his symptoms would worsen as an outpatient due to hyperglycemic periods related to poor adherence to his current diabetes regimen. Upon admission, the patient's glucose level (270 mg/dL) and A1C (8.4 mg/dL) were both not at goal. The decision was made to reinforce tighter glycemic control with basal and rapid acting insulin targeting an HbA1c goal of <7%. Lisinopril was also increased to 10 mg daily for better blood pressure control.

Although persistent, the number of vomiting episodes declined throughout the hospital admission. On day four, following a Gastroenterology (GI) consult, the patient was started on buspirone 10 mg three times a day for greater symptom control based on previously published research investigations demonstrating the futility of buspirone in the relief of symptoms associated with both rapid and delayed gastric emptying [12]. It was unclear whether the patient was given buspirone for previously diagnosed gastroparesis or dumping syndrome, as the last gastric emptying study was positive for rapid gastric emptying. The patients' symptoms significantly resolved after three days of treatment and he was discharged on November 07th, 2018. After several ambulatory care visits, the patient's records show metoclopramide and famotidine were discontinued. Consequently, the patient has not been experiencing any symptoms. As mentioned, metoclopramide was most likely discontinued due to tachyphylaxis, which could explain why his symptoms were no longer under control when taking it. As of December 28th, 2019, the patient was still taking buspirone in addition to omeprazole 40 mg once daily, with no complaints of returned symptoms.

Discussion

Diabetic neuropathy can disturb gastric emptying resulting in either delayed or accelerated gastric emptying. It is postulated that rapid gastric emptying in diabetes is due to early vagal damage involving only the distal end of the nerve. However, when the entire nerve is affected, slowing of gastric transit or gastroparesis can occur [13,14]. Early observations demonstrated the use of intravenous dextrose to alleviate gastric hunger contractions in healthy patients and provided the earliest association between acute hyperglycemia and gastric motor activity [15]. It has now been confirmed that marked acute hyperglycemia delays gastric emptying substantially in both healthy and diabetic patients. Emptying is slowed even at physiological degrees of hyperglycemia and is accelerated during insulin-induced hypoglycemia [16]. Given that hyperglycemia delays gastric emptying, it is recommended to defer gastric emptying testing until relative euglycemia is achieved and optimal glycemic control in patients with diabetes is warranted to minimize the effects of hyperglycemia, causing this delayed emptying.

In our patient case, it was noted that his presumed gastroparesis could potentially worsen after discharge, possibly related to poor medication adherence. The GI team proposed the likelihood of the patient having an alternative gastrointestinal disorder and suggested performing additional tests. Making the distinction between gastroparesis and FD can be challenging due to overlapping symptoms of epigastric fullness, bloating, nausea and vomiting. The difficulty in distinguishing among these two entities may result in misdiagnosis, ultimately resulting in the initiation of ineffective or even harmful therapy. It is possible that the healthcare team initially assumed our patient presented with gastroparesis as he also was diagnosed with diabetes. However, considering this patient experienced rapid gastric emptying during a past admission, it was more likely he was experiencing FD [11]. The patient was initiated on 10 mg of buspirone three times daily based on the published results of the Efficacy of Buspirone, a Fundus-Relaxing Drug, in Patients with Functional Dyspepsia trial [17]. The results of this study showed that buspirone reduced symptoms found in patients with FD. Much like findings in this study, our patient's symptoms resolved after taking buspirone. Buspirone was indicated for this patient for questionable overlapping of gastroparesis and FD etiology. The buspirone was successful most likely due to the commonality of having impairment in accommodation, which is present in both disorders. Therefore, the success of the treatment cannot be used as a confirmation of his GP diagnosis, but rather further suggests that this patient may have FD.

In the Efficacy of Buspirone, a Fundus-Relaxing Drug, in Patients with Functional Dyspepsia trial, the influence of buspirone on symptoms, gastric emptying rate, gastric accommodation, and sensitivity to gastric distention in functional dyspepsia patients was studied. This randomized, double-blind, placebo-controlled, crossover study, contained a sample size of seventeen patients. The study consisted of two-week run in periods, followed by two four-week treatment periods. Each of the treatment periods was separated by a two-week washout. The treatment consisted of buspirone 10 mg three times daily 15 min before meals *vs.* placebo, also given three times daily, 15 min before meals. The primary end point was improvement in dyspepsia symptom severity scores after four weeks of treatment with buspirone. The secondary endpoints assessed the effects of treatment on meal-related symptoms severity scores, solid and liquid gastric emptying rates, gastric compliance, thresholds during balloon distension, and meal induced gastric accommodation, before and four weeks after treatment with buspirone [17].

In the study, patients were required to complete a Dyspepsia Symptom Severity (DSS) score at the end of the run-in and washout periods, and at the end of each treatment period. Patients scored the intensity of eight specific dyspeptic symptoms: Epigastric pain, postprandial fullness, upper abdominal bloating, early satiation, nausea, vomiting, and epigastric burning and belching. The DSS score was defined as the sum of all eight items. The study concluded, four weeks of treatment with 5-HT1A agonist buspirone 10 mg three times daily improved overall severity of symptoms of dyspepsia and individual symptoms of postprandial fullness, early satiation, and upper abdominal bloating significantly, whereas no significant difference occurred after placebo. Buspirone 10 mg three times daily did not alter the rate of gastric emptying of solids or sensitivity to gastric distention, but it significantly increased gastric accommodation, compared with placebo, and delayed gastric emptying of liquids [17].

In addition to medication changes, our patient's symptoms were potentially resolved due to the modifications of his diabetes regimen, which resulted in significant glycemic control. As of his last clinic visit on December 28th, 2019, his HbA1c was 7.1%, compared to his baseline HbA1c of 8.4% that he initially took in October of 2018. The patient continues to be prescribed buspirone with no dose changes since his visit in December of 2019. It is difficult to determine if buspirone alone relieved the patient from symptoms, or if it was due to a multitude of interventions. These interventions include glycemic control, discontinuation of metoclopramide, or initiation of buspirone and omeprazole. Further testing was never done to conclude if gastroparesis was the definitive cause for his history of nausea or vomiting, or to determine if another gastrointestinal disorder, such as FD, was responsible. Notably, no hospital encounters since the last occurrence were noted in the patient encounter summaries.

One of the major limitations of current first line therapies, such as metoclopramide, domperidone and erythromycin is tachyphylaxis. Even if the use of these agents is shown to be beneficial, over time these therapeutic effects could diminish, and so finding equally therapeutic alternatives is crucial [1,4]. Studies have shown that gastric accommodation plays a significant role in symptomatology within patients experiencing FD and gastroparesis. In addition, buspirone may be beneficial in patients requiring treatment for a longer duration. Although, the efficacy of buspirone prescribed greater than 3 to 4 weeks has not been demonstrated in controlled trials, in one study of long-term use, 264 patients were treated with buspirone for one year without negative effects [18].

Conclusion

The rationale for using buspirone in the treatment of gastroparesis and FD is secondary to impaired gastric accommodation. Gastric accommodation is believed to be present in about 50% of cases of gastroparesis and contributes to several of its symptoms including nausea, vomiting and early satiety. In FD, the predominant sensation of early satiety has also been proven to be closely associated with impaired accommodation, although it is also reported in 25% of patients with delayed gastric emptying. Nausea and vomiting, the cardinal symptoms of gastroparesis, develop in at least 20% to 50% of FD patients [6]. Thus, by restoring gastric accommodation, through inhibition of the 5-HT1A receptor, at doses of 30 mg or higher, could treat both gastroparesis and FD. As a result, buspirone may help relieve the symptoms associated with gastric accommodation as it showed to be an effective, safe, and well-tolerated therapeutic option for this patient.

A newly defined interest in the pathophysiology behind gastroparesis provides promise for a new era of treatment options including buspirone. Some limitations of the previous studies mentioned included the small sample size. Further studies, with larger populations, need to be performed to consider buspirone an effective agent for the treatment of gastroparesis. Currently, Buspirone for Early Satiety and Symptoms of Gastroparesis (BESST), a multicenter, randomized, placebo-controlled, double-blinded trial, is currently under investigation. This trial will be further evaluating the use of Buspirone in Gastroparesis [19]. We hope that results from the BESST trial, which contains a large population size, will shed more light on the use of buspirone in this patient population and might aid in the decision of including it as part of the treatment plan.

References

1. Camilleri M, Parkman HP, Shafi MA, Abell TL, Gerson L. Clinical guideline: Management of gastroparesis. Am J Gastroenterol. 2013;108(1):18-37.
2. Parkman HP. Idiopathic gastroparesis. Gastroenterol Clin North Am. 2015;44(1):59-68.
3. Camilleri M, Bharucha AE, Farrugia G. Epidemiology, mechanisms, and management of diabetic gastroparesis. Clin Gastroenterol Hepatol. 2011;9(1):5-12.
4. Vavricka SR, Greuter T. Gastroparesis and dumping syndrome: Current concepts and management. J Clin Med. 2019;8(8):1127.
5. Kindt S, Tack J. Impaired gastric accommodation and its role in dyspepsia. Gut. 2006;55(12):1685-91.
6. Kim BJ, Kuo B. Gastroparesis and functional dyspepsia: A blurring distinction of pathophysiology and treatment. J Neurogastroenterol Motil. 2019;25(1):27-35.
7. Paul MM, Brian EL, Christopher NA, Robert AE, Colin WH, Nimish V. ACG and CAG Clinical guideline: Management of dyspepsia. Am J Gastroenterol. 2017;112(7):988-1013.
8. Longstreth G, Lacy B. Functional dyspepsia in adults. UpTo Date. 2019.
9. Tack J. Prokinetics and fundic relaxants in upper functional GI disorders. Curr Opin Pharmacol. 2008;8(6):690–6.
10. Van Oudenhove L, Kindt S, Vos R, Coulie B, Tack J. Influence of buspirone on gastric sensorimotor function in man. Aliment Pharmacol Ther. 2008;28(11-12):1326–33.
11. Nee J, Iturrino J. Gastroparesis Versus functional dyspepsia: Still running on emptying. Dig Dis Sci. 2019;64(5):1064-6.
12. Radetic M, Gabbard S. Buspirone for the management of functional dyspepsia with rapid gastric emptying. ACG Case Rep J. 2019;6(11):e00280.
13. Franklin cardiovascular associates PA, Gastroparesis part 3 and dumping syndrome. 2019.
14. Kim BJ, Kuo B. Gastroparesis and functional dyspepsia: A blurring distinction of pathophysiology and treatment. J Neurogastroenterol Motil. 2019;25(1):27–35.
15. Stunkard AJ, Wolff HG. Studies on the physiology of hunger. I. The effect of intravenous administration of glucose on gastric hunger contractions in man. J Clin Invest. 1956;35(9):954–63.
16. Chinmay S, Christopher K, Karen L, Horowitz M. Relationships between gastric emptying, postprandial glycemia, and incretin hormones. Diabetes Care. 2013;36(5):1396-405.
17. Tack J, Janssen P, Masaoka T, Farré R, Oudenhove LV. Efficacy of buspirone, a fundus-relaxing drug, in patients with functional dyspepsia. Clin Gastroenterol Hepatol . 2012;10(11):1239-45.
18. Buspirone [package insert]. Princeton, NJ: FDA; November 2010. Accessed June 25, 2020.
19. National Institute of Diabetes and Digestive and Kidney Diseases. Buspirone for early satiety and symptoms of gastroparesis: A multicenter, randomized, placebo-controlled, double-masked trial (BESST).