Philadelphia College of Osteopathic Medicine
DigitalCommons@PCOM

PCOM Physician Assistant Studies Student Scholarship | Student Dissertations, Theses and Papers

2019

Is Metoclopramide Effective in Treating Symptoms in Diabetic Gastroparesis?

Prachi Patel
Philadelphia College of Osteopathic Medicine

Follow this and additional works at: https://digitalcommons.pcom.edu/pa_systematic_reviews

 Part of the Endocrinology, Diabetes, and Metabolism Commons

Recommended Citation

Patel, Prachi, "Is Metoclopramide Effective in Treating Symptoms in Diabetic Gastroparesis?" (2019). *PCOM Physician Assistant Studies Student Scholarship*. 483.
https://digitalcommons.pcom.edu/pa_systematic_reviews/483

This Selective Evidence-Based Medicine Review is brought to you for free and open access by the Student Dissertations, Theses and Papers at DigitalCommons@PCOM. It has been accepted for inclusion in PCOM Physician Assistant Studies Student Scholarship by an authorized administrator of DigitalCommons@PCOM. For more information, please contact library@pcom.edu.

Is Metoclopramide Effective in Treating Symptoms in Diabetic Gastroparesis?

Prachi Patel PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences - Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

December 14, 2018

ABSTRACT

Objective: The objective of this selective EBM review is to determine whether or not is metoclopramide effective in treating symptoms in diabetic gastroparesis?

Study Design: Systematic review of 1 controlled randomized double blinded study, 1controlled randomized open label study, and 1 controlled open label case analysis published in peer reviewed journals between 2012-2014, all in English language.

Data Sources: 1 randomized double blinded study, 1 randomized open label study, and 1 case analysis comparing symptom reduction of gastroparesis after the intervention of nasal and oral metoclopramide compared to placebo controls. These sources were found using PubMed and OVID.

Outcomes Measured: Patients graded their symptoms on a scale and graded the severity of each symptom after the use of nasal and oral metoclopramide. The studies gave patients different scales to measure the severity of each symptom which included a Symptom Assessment Questionnaire (SAQ), Gastroparesis Cardinal Symptom Index Daily Diary, and a Clinical Patient Grading Assessment Scale (CPGAS).[5,6,7]

Results: Conclusively, the studies did not show a reduction in symptoms after the intervention for gastroparesis in diabetic patients. Only one study demonstrated symptom reduction to be statistically significant while the other two studies did not.

Conclusions: The use of metoclopramide did not show an improvement in gastroparesis symptoms as assessed by patients after the use of the medication from these studies. More RCT need to be done to prove this scientifically rather than through patient report due to bias or misunderstanding of scoring and through a trial using same comparison groups for a longer duration.

Key Words: Gastroparesis, Metoclopramide

INTRODUCTION

Diabetes is the seventh leading cause of death in the United States and is prevalent in about 30.3 million Americans as of 2015.[1] Diabetes as the primary medical condition results in 34.6 million health care visits in the past year.[1] The health care cost of a diabetes in 2017 in the United States was about $327 billion.[1] Type 1 Diabetes is caused by a deficiency in insulin due to autoantibodies that form and attack the pancreatic islet beta cells that develops usually before the age of 20, resulting in hyperglycemia. Type 2 diabetes is mainly due to insulin resistance, insulin insufficiency, and elevated hepatic glucose production over time, also resulting in hyperglycemia, and commonly seen with obesity.[1] The prevalence of diabetes is increasing drastically with 50 to 65% of patients with diabetes mellitus also having a diagnosis of gastroparesis.[2] Diabetic gastroparesis is more prevalent in type 1 diabetics, but it is also seen in type 2 diabetics as well.

Gastroparesis is delayed gastric emptying that is seen in both type 1 and type 2 diabetes. This results in nausea, vomiting, belching, abdominal pain, heart burn, and early satiety. The exact etiology of diabetic gastroparesis is unknown and there is no ultimate cure other than to provide some relief of symptoms with changes in diet and using certain medications such as metoclopramide.[3] It is suggested that gastroparesis occurs due to damage to the vagus nerve which controls the movement of food through the digestive tract.[3]

Metoclopramide, a prokinetic, increases muscle contractions in the digestive tract. Other than gastroparesis, Metoclopramide's other uses involve the treatment of heartburn caused by gastroesophageal reflux disease.[3,4] Other treatments to manage gastroparesis include controlling diet which is usually the initial step. Fatty, spicy, and acidic foods, and carbonated drinks should be avoided.[4] This, however, only works for mild cases of gastroparesis. Hydration is key in

patients who have vomiting symptoms. Nutritional deficiencies can also arise in this specific group of patients due to vomiting episodes and resistance to eat due to nausea. Due to these side effects of gastroparesis, replenishing micronutrients is essential. Other treatments for targeting other symptoms of gastroparesis include erythromycin, prochlorperazine, diphenhydramine, and ondansetron. Refraining from smoking is also insisted in gastroparesis patients. A nonconventional method includes acupuncture.[4] Lastly, surgical treatment is reserved for patients who are unable to tolerate any types of food at all, which includes a jejunostomy tube.[4]

Diabetic patients struggle to maintain their quality of life with trying to balance diet, exercise, frequent doctor and pharmacy visits, insurance difficulties, and treatment adherence. Diabetes causes an increase in glucose in the body which delays emptying food from the stomach to the intestines which causes an arousal of symptoms. Gastroparesis adds further stress to a diabetic patient decreasing their quality of life furthermore. Since so much of the population if affected by diabetes and its immense list of complications, one being gastroparesis, it is essential for all healthcare providers to be knowledgeable so that proper guidance and effective treatment can be recommended for patients. This paper evaluates the effectiveness of metoclopramide for gastroparesis symptoms in diabetic patients, compared to nasal and oral forms of metoclopramide, as well as to the placebo control.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not is Metoclopramide effective in treating symptoms in diabetic gastroparesis?

METHODS

This selective EBM review examined three studied which included 1 randomized double blinded study, 1 randomized open label study, and 1 open label case analysis comparing

symptom reduction of gastroparesis after the intervention of nasal and oral metoclopramide compared to placebo controls.[5,6,7] The population included male and female patients older than 18 years of age with a diagnosis of diabetes and gastroparesis. The intervention used in each of the studies was metoclopramide 14 mg and 20 mg nasal spray, as well as oral metoclopramide 10 mg.[5,6,7] Treatment groups received the nasal metoclopramide and the control group received the oral metoclopramide or placebo. The outcomes measured in each was whether there was a reduction in symptoms of gastroparesis after the intervention of metoclopramide for patients experiencing gastroparesis, furthermore if there was a better prognosis when comparing nasal to oral metoclopramide. All studies were published in the English language and were published between 2012 through 2014. The studies were found using two keywords "Gastroparesis" and "Metoclopramide" through PubMed and OVID. Articles were selected based on their relevance to the clinical question and had patient oriented outcomes (POEMS). Inclusion criteria included studies that were randomized, controlled, double blind, open label, and case analysis studies that measured the effectiveness of metoclopramide in gastroparesis patients. It also included patients taking metoclopramide or patients who had a diagnosis of gastroparesis. Articles written over 10 years ago and patients under the age of 18 were excluded as part of the exclusion criteria. Statistics reported were p-values, relative benefit increase (RBI), numbers needed to treat (NNT), and absolute benefit increase (ABI). The demographics and characteristics of the individuals included in these studies are displayed in Table 1.

Table 1 – Demographics & Characteristics of included studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Parkman[5] HP, 2012	Open - Label Case Analysis	100	>18 years of age	Patients 18 years of age and older receiving or having received metoclopramide treatment as part of their regular clinical care, and able to provide informed consent to participate in the study.	Patients with a fasting glucose >280 mg/dL did not meet the standards to be a candidate.	0	Metoclopramide
Parkman[6] HP, 2015	Double Blind RCT	225	18-75 years of age	18 to 75 years of age with type 1 or type 2 DM with a diagnosis of gastroparesis, and who had a mean daily GCSI–DD score between 2-4 for the 7 days before the randomization visit (day 0) and were willing to discontinue treatment for diabetic gastroparesis.	Subjects with a mean GCSI–DD total score of less than 2.0 or greater than 4.0 during the washout period were excluded.	2	Metoclopramide 14 mg Nasal Spray
Parkman[7] H, 2014	Open-Label RCT	89	18-82 years of age	Men, non-pregnant, non-lactating women aged 18 years or older with a diagnosis of Type 1 or Type 2 diabetes and diabetic gastroparesis who were willing to discontinue current gastroparesis treatment for at least 7 days before dosing until the end of the 6-week study. Baseline requirement of a score between 8-20 on SAQ and IAQ scale with at least 2/6 symptoms on the SAQ and IAQ rated moderate or higher (≥2) for frequency and severity was required.	Patients with abnormal chemistry or hematology parameters (with the exception of plasma glucose), and an estimated creatinine clearance of <40 mL/min were excluded.	7	Metoclopramide 20 mg Nasal Spray

OUTCOMES MEASURED

Throughout these studies, patients graded their symptoms on a scale based on change whether they improved, worsened, or stayed the same after the use of metoclopramide. In one study, a Clinical Patient Grading Assessment Scale (CPGAS) was used.[5] In another study, patients kept track of their symptoms by recording the data in a Gastroparesis Cardinal Symptom Index Diary.[6] In the last study, investigators assessed patient's symptoms and their severity through an Investigator's Assessment Questionnaire. after patients had filled out a Symptom Assessment Questionnaire (SAQ).[7]

RESULTS

All three studies used an intervention of metoclopramide whether it was in a nasal or oral form. Two studies used nasal metoclopramide as interventions comparing it to placebo or a control. One study, a case analysis, used an intervention of metoclopramide but had no control or comparison group. All studies used participants above the age of 18 including men and women with gastroparesis symptoms. In all three studies, patients under the age of 18 were excluded. Subjects with high glucose readings were also excluded to maintain proper glycemic levels, since a side effect of metoclopramide includes hyperglycemia.[5,6,7] Parkman's 2015 double blind RCT excluded patients whose gastroparesis symptoms were too mild, as metoclopramide was not needed, or to severe, to maintain safety form adverse effects.[6] In this double blind RCT, two subjects did not complete the experiment due to withdrawal of consent and another subject having a history of chronic pancreatitis.[6] In Parkman's 2014 open label RCT, 92.1% subjects completed the study, and seven subjects withdrew from the study due to side effects.[7]

Parkman's 2014 RCT open label study evaluated the change in symptoms from baseline with the intervention of nasal metoclopramide 20 mg and compared it to oral metoclopramide 10

mg at six study sites across the United States.[7] The intervention of nasal metoclopramide 10 mg was also used in this study, however, this paper will solely focus on the nasal metoclopramide 20 mg compared to the oral metoclopramide 10 mg. Eighty-nine diabetic participants were assessed in this study for six weeks and were given metoclopramide four times a day. A symptom assessment questionnaire (SAQ) was used where patients rated the symptom severity before, during, and after the treatment. Symptoms included nausea, vomiting, anorexia, bloating, early satiety, and meal tolerance. A score between 0 to 4 was given. Then, the investigator's assessment questionnaire (IAQ) was used by investigators to rate the severity for each patient as well by interviewing each patient. The mean total symptom score (TSS) reduced about 13 points for nearly all patients from baseline after 1 week of treatment. The data showed that 97.1% of the participants who received nasal metoclopramide 20 mg and 88.9% who received oral metoclopramide 10 mg responded to the treatment.[7] The nasal 20 mg metoclopramide group had a confidence interval of (-7.1,-0.5) with a p-value of 0.026 as shown in Table 2.[7]

Table 2: Comparison of Efficacy through Mean Change from Baseline to Outcome

Treatment Metoclopramide	N	Baseline Mean	Mean change from baseline	95% CI	p-value
Nasal 20 mg[7]	35	21.3	-18.0	(-7.1, -0.5)	0.026
Oral 10 mg[7]	18	22.9	-14.3	N/A	N/A

The data from the study was calculated to get the number needed to treat (NNT) which was 13 as shown in Table 3. 13 people need to be treated with metoclopramide in order to have one successful outcome in reducing symptoms of gastroparesis.

Table 3: Statistical Analysis of Parkman's Efficacy in Improving Symptoms

NNT	RBI	ABI
13	0.092	0.082

Parkman's 2015 RCT double blinded study used 14 mg nasal metoclopramide as its intervention and compared it to a placebo. This study used participants between the age of 18 to 75 who also had a diagnosis of diabetes and a gastroparesis similar to Parkman's 2014 RCT open label study. These 225 participants were monitored in the United States at various gastroenterology or mixed specialty practices that treated gastroparesis.[6] Four symptoms were monitored throughout this study which included nausea, bloating, early satiety, and upper abdominal pain.[6] This study also used nasal metoclopramide 10 mg, however, this paper will focus only on the placebo compared to the nasal 14 mg metoclopramide. Subjects recorded symptom severity on the Gastroparesis Cardinal Symptom Index Daily Diary.[6] Compliance of males completing daily diary recordings was 90% and 86% for females.[6] They were required to grade each symptom from 0 to 5. The study did not show a confidence interval however a p-value of 0.3005 comparing the placebo to the 14mg metoclopramide was reported which is not statistically significant.[6] The change from baseline to end of the study showed a mean and standard deviation of -1.2(0.94) compared to the placebo -1.0(0.89).[6] This study also focused on the changes in symptoms between males and females. Women with nasal metoclopramide had more improvements with symptoms reported by the change from baseline to week 4 with a mean and standard deviation of -1.3(0.98) as compared to males -0.9(0.78). Males seemed to have a greater response to the placebo with a mean and standard deviation of -1.4(0.98).[6] This data is shown in Table 4.

Table 4: Mean Gastroparesis Cardinal Symptom Index-Daily Diary (GCSI-DD) Total Score Change from Baseline to Week 4[6]

	Placebo (N=95)	MCP 14 mg Nasal (N=96)
Baseline, mean (SD)	2.8(0.57)	2.8(0.062)
Week 4, mean (SD)	1.8(1.00)	1.7(0.90)
Change from baseline to week 4	-1.0(0.89)	-1.2(0.94)
p-value	N/A	0.3005

Women -Baseline, mean (SD)	2.7 (0.54)	2.9(0.62)
Male -Baseline, mean (SD)	2.9(0.63)	2.5(0.56)
Women - Week 4, mean (SD)	1.9 (1.02)	1.7(0.94)
Men - Week 4, mean (SD)	1.4(0.84)	1.7(0.79)
Women - Change from baseline to week 4	-0.8(0.79)	-1.3(0.98)
Men - Change from baseline to week 4	-1.4(0.98)	-0.9(0.78)

The last study, Parkman's case analysis, focused on 100 participants who were regularly taking metoclopramide for gastroparesis, 34 of these patients had a diagnosis of diabetes.[5] Patients assessed their symptoms using the Clinical Patient Grading Assessment Scale from a score of -3 to 3. The study stated that 53% of the participants had improvement with taking metoclopramide with a p-value of 0.83.[5] This study further investigated side effects and found that 64% of the participants reported side effects to metoclopramide.[5] Side effects included anxiety, akathisia, fatigue, tremors, depression, dystonia, seizures, and tardive dyskinesia. The study reported that side effects were often more reported in the 77% of non-diabetic patients rather than diabetic gastroparesis patients.[5]

The other two studies also reported side effects of headaches, fatigue, nausea, vomiting, dysgeusia, drowsiness, and restlessness. Parkman's RCT open label study found an increase in side effects in oral 10 mg metoclopramide compared to nasal 20 mg metoclopramide. There were no reported deaths in any of the studies. The greatest side effects reported conclusively from all three studies were those affecting the central nervous system. The complaints reported by patients in each study listed by frequency are shown more thoroughly by various body systems in Table 5.

Table 5: Adverse Effects reported by frequency of participants in each study

Adverse Effects	Parkman's RCT Open Label[7]	Parkman's RCT Double Blind[6]	Parkman's Case Analysis[5]
Nervous System (HA, Dizziness, akathisia, tremors, tardive dyskinesia, dystonia, confusion, seizure, dysgeusia)	1	24	31
Psychiatric (depression, anxiety)	0	0	15

Gastrointestinal (diarrhea, vomiting, nausea)	3	6	0
Metabolic (hyperglycemia, hypoglycemia)	0	6	0
Respiratory (cough, epistaxis, cough, rhinorrhea, throat discomfort)	0	14	0
Infections (URI)	0	3	
General (fatigue)	0	6	9
Skin (rash)	1	0	
Miscellaneous	0	0	9

DISCUSSION

There were many limitations seen in these studies. All three studies used questionnaires for patients to fill out as their main source of composing and collecting data. The scoring range scale in each of the studies was different making it difficult to align the data together.

Metoclopramide, brand name Reglan, is a dopamine 2 receptor antagonist, a 5-HT4 agonist, and a weak HT3 receptor agonist, which the FDA has approved for the treatment for gastroparesis for 12 weeks, longer if the benefits are greater than the risks.[5] However, Metoclopramide has a black box warning for tardive dyskinesia.[3] Parkman's 2012 case analysis also failed to report the duration of the study making it not a reliable source to administer treatment in a patient. Furthermore, the open label case analysis reported adverse effects of tardive dyskinesia and many other central nervous system adverse side effects. CNS side effects cause hesitation in administering treatment in patients, especially those that involve movement disorders like tardive dyskinesia.

Metoclopramide is the only approved treatment for gastroparesis by the FDA and is easily accessible to most patients through health insurances.[3] It is also easily available

throughout the United States with a prescription. Oral tablet form is more common than nasal metoclopramide.[4] Injection form is also available.

CONCLUSION

Other resources have shown that metoclopramide is the only approved treatment for gastroparesis. However, these three studies did not show collective data to show that metoclopramide is effective in treating symptoms in gastroparesis. These studies also showed adverse effects of metoclopramide, some of which included seizures, tardive dyskinesia, and other movement disorders which makes treating a patient with this drug highly questionable. Further investigation showed that only 2 patients developed tardive dyskinesia from Parkman's 2012 case analysis.[5] The studies showed that metoclopramide is safe and moderately tolerable in most patients, and less side effects when used in diabetic patients. No deaths occurred in the trials either. This drug has FDA approval which allows for more use by physicians and less risks when used in patients, however, the data conclusively in all studies do not support evidence to prove the efficacy of metoclopramide. Parkman's 2012 case analysis had no comparison group and used any dose of metoclopramide and any duration of time metoclopramide was being used by patients. Parkman's 2015 study compared to a placebo while Parkman's 2012 group compared to another dose of metoclopramide. There was no common comparison group in any of the studies and only Parkman's 2014 study showed to be statistically significant. Further studies should be conducted specifically in groups of people who have developed tardive dyskinesia, seizures, akathisia, or other CNS adverse effects to see if the therapeutic benefit of metoclopramide does in fact outweigh the risks, and trials that are longer in duration.

REFERENCES

1. Diabetes Basics. Cost of Diabetes. *American Diabetes Association.* http://diabetes.org/advocacy/news-events/cost-of-diabetes.html. Accessed October 5, 2018.

2. National Center for Health Statistics. Centers for Disease Control and Prevention. https://www.cdc.gov/nchs/fastats/diabetes.htm. Published May 3, 2017. Accessed October 5, 2018

3. Camelleri M. Treatment of gastroparesis. UpToDate. https://www-uptodate-com.ezproxy.pcom.edu/contents/treatment-of-gastroparesis?search=metoclopramide&source=search_result&selectedTitle=2~148&usage_type=default&display_rank=1. Published September 24, 2018. Accessed October 5, 2018.

4. Gastroparesis. Mayo Clinic. https://www.mayoclinic.org/diseases-conditions/gastroparesis/diagnosis-treatment/drc-20355792#! Published March 8, 2018. Accessed December 1, 2018

5. Parkman HP, Carlson MR, Gonyer D. Metoclopramide nasal spray is effective in symptoms of gastroparesis in diabetics compared to conventional oral tablet. *Neurogastroenterology & Motility.* 2014;26(4):521-528. http://onlinelibrary.wiley.com/doi/10.1111/nmo.12296/abstract. doi:10.1111/nmo.12296.

6. Parkman HP, Carlson MR, Gonyer D. Metoclopramide nasal spray reduces symptoms of gastroparesis in women, but not men, with diabetes: Results of a phase 2B randomized study. *Clinical gastroenterology and hepatology: the official clinical practice journal of the American Gastroenterological Association.* 2015;13(7):1263.e1. http://www.ncbi.nlm.nih.gov/pubmed/25576687. doi: 10.1016/j.cgh.2014.12.030.

7. Parkman H, Mishra A, Jacobs M, et al. Clinical response and side effects of metoclopramide: Associations with clinical, demographic, and pharmacogenetic parameters. *Journal of Clinical Gastroenterology*. 2012;46(6):494-503. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&NEWS=n&CSC=Y&PAGE=fulltext&D=ovft&AN=00004836 -201207000-00012. doi: 10.1097/MCG.0b10