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CASE REPORT | FUNCTIONAL GI DISORDERS

Mirtazapine for Refractory Gastroparesis

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ABSTRACT

Gastroparesis is a chronic condition of delayed gastric emptying in the absence of mechanical outlet obstruction. We report a 47-year-old African American woman with diabetic gastroparesis who presented with intractable nausea, vomiting, and decreased oral intake with electrolyte disturbances. The patient's symptoms were difficult to control with antiemetic and conventional prokinetic agents, and she was started on mirtazapine 15 mg nightly. She experienced an almost complete symptom relief and was able to tolerate solid food within 24–48 hours. We highlight the role of mirtazapine, a 5-HT_{1a} agonist, as an effective therapy for refractory gastroparesis.

INTRODUCTION

Gastroparesis causes delayed gastric emptying in the absence of gastric outlet obstruction. Common causes of gastroparesis include diabetes mellitus (DM), gastrointestinal infection, surgical intervention, and idiopathic.[1] DM is the most frequent systemic disease associated with gastroparesis. In a population-based, historical cohort study, the cumulative proportions of patients developing gastroparesis over a 10-year time period were 5.2% in type 1 DM, 1.0% in type 2 DM, and 0.2% in controls.[2] The symptoms of gastroparesis include nausea, vomiting, upper abdominal pain, postprandial fullness, and bloating, which may lead to multiple frequent hospital admissions.[3] The gold standard for diagnosis is solid-phase gastric scintigraphy; gastric retention of >10% at 4 hours is diagnostic.[4]

Medical therapy is primarily focused on a combination of prokinetic agents that work on dopamine receptors (metoclopramide and domperidone) and antiemetic agents (ondansetron, promethazine, and prochlorperazine).[1,3] Metoclopramide, a commonly used prokinetic, has a "black box" warnings from the US Food and Drug Agency because of the risk of extrapyramidal side effects.[5] Erythromycin has the potential for diarrhea and QT-prolongation and is commonly associated with tachyphylaxis. Implantation of a gastric electrical stimulator is recommended after failure of conventional medical therapy for 1 year, but results have been inconsistent.[6] Despite these therapeutic options, many patients still experience debilitating symptoms. Mirtazapine, a tetracyclic antidepressant with 5-HT_{1a} receptor agonist activity in the central and peripheral nervous system, has been used to alleviate symptoms of gastroparesis.[7–12] We describe a patient with refractory gastroparesis secondary to DM who had symptomatic relief after starting mirtazapine 15 mg nightly. In contrast to previous reports describing the use of mirtazapine in patients with idiopathic, postsurgical, postinfectious, neurological, or multifactorial gastroparesis, our patient had gastroparesis attributed only to DM.

CASE REPORT

A 47-year-old African American woman with insulin-requiring type 2 DM complicated by gastroparesis, retinopathy, and neuropathy presented with a 2-day history of intractable nausea and vomiting, diffuse crampy abdominal pain, and postprandial fullness. She had no psychiatric problems. She had multiple hospitalizations over the preceding 6–12 months for similar episodes, and an esophagogastroduodenoscopy performed during one of these hospitalizations had ruled out gastric obstruction. A gastric emptying study performed within the preceding year, while she was off narcotic and anticholinergic medications and her blood glucose was in the normal range, showed 60% retention after 4 hours. She was instructed to eat small frequent meals, and

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appropriate dietary modifications were tried with minimal response. Her DM was well controlled (HbA1C 6.0%; fasting blood glucose 75–138 mg/dL) with basal and prandial insulin. The patient had previously been treated with intravenous and oral ondansetron, promethazine, and prochlorperazine. Before her current hospitalization, she had been taking metoclopramide 5 mg 3 times daily but had remained symptomatic with nausea and vomiting.

During the current admission, laboratory studies were unremarkable except for potassium level 3.2, which was appropriately corrected, and an abdominal x-ray was unremarkable. She was started on intravenous metoclopramide 30 mg daily and ondansetron 4 mg every 6 hour. Owing to uncontrolled symptoms and lack of response to metoclopramide, she was started on mirtazapine 15 mg nightly, and metoclopramide and ondansetron were discontinued. Within 2 days, she reported dramatic improvement of nausea and vomiting and was able to tolerate liquid diet followed by solid food. She reported drowsiness in the morning after starting mirtazapine, which improved after being given earlier in the evening around 6 PM. The patient was discharged on mirtazapine 15 mg nightly and ondansetron 4 mg as needed for nausea and vomiting.

DISCUSSION

Because refractory gastroparesis can be debilitating, it is important to identify potential new therapies. Mirtazapine acts on multiple 5-hydroxytryptamine (5-HT; serotonin) receptor subtypes, including 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}, and 5-HT_3.[13] In functional dyspepsia, it acts on central and peripheral 5-HT_{1A} receptors, leading to gastric fundus relaxation, better symptom control, and improved quality of life.[14] It is also an antagonist at 5-HT_3 receptors, which may account for its antiemetic effect.[15]

In a single-center prospective, open-label trial of 30 patients with refractory gastroparesis, mirtazapine significantly ($P < 0.001$) improved nausea and vomiting at 2 and 4 weeks compared with baseline. This cohort included 4 patients with DM, all of whom responded. However, the presence or absence of psychiatric disease was not taken into account when enrolling patients; this is a potential limitation because the improvement of mood could have altered the observed effect.[11] Kim et al reported a patient with depression and type 1 DM who had refractory gastroparesis for 7 months and had complete resolution of symptoms with mirtazapine.[9] Similarly, Kundu et al reported a patient with postinfectious gastroparesis in whom symptoms improved with mirtazapine.[10] Mirtazapine also reduces tube feed residuals and postoperative gastroparesis.[7,8] A randomized, double-blind study evaluated gastric emptying, satiation, and postprandial symptoms following a nutrient load in healthy volunteers after 14 days of mirtazapine or nortriptyline. It did not show statistically significant effects of mirtazapine or nortriptyline on gastric emptying compared with placebo ($P = 0.34$).[16] However, this study evaluated healthy volunteers, not patients with gastroparesis, and used a nutrient drink test to induce symptoms. It also used the [^{13}C]-octanoic acid breath test to measure gastric emptying rather than gastric scintigraphy.

Mirtazapine has been used in idiopathic, postsurgical, postinfectious, and neurological and diabetic gastroparesis with or without comorbid neurological or psychiatric conditions. A population-based cohort study from Olmsted County, Minnesota, estimated the prevalence of psychiatric illnesses including anxiety, depression, and eating disorders in patients with gastroparesis at 30%.[17] Mirtazapine's antidepressant properties could have led to symptomatic improvement observed in previous case reports. By contrast, our patient had no history of psychiatric/central neurological illnesses and no other apparent cause of gastroparesis except DM. Therefore, we believe the beneficial effect of mirtazapine in our patient was independent of its antidepressant effect. This case highlights the use of mirtazapine as a treatment for refractory diabetic gastroparesis.

As mirtazapine is "off-label" for gastroparesis, Malamood et al showed that it could only be used in a select number of patients because of side effects of drowsiness and lethargy.[11] Based on our experience, we suggest that patients be followed up weekly for at least the first 2 months after initiation of treatment to monitor adverse effects. Large-scale, comparative, and controlled studies are required to further elucidate the safety and efficacy of mirtazapine in patients with gastroparesis.

DISCLOSURES

Author contributions: HK Marella and N. Saleem wrote and revised the manuscript, and K. Olden revised the manuscript and approved the final version. HK Marella is the article guarantor.

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