Original Article

Effect of Mirtazapine on Gastric Emptying in Patients with Cancer-associated Anorexia

N Kumar, Sukanta Barai, S Gambhir, N Rastogi[1]

Departments of Nuclear Medicine and [1]Radiotherapy, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India

Abstract

Background/Aims: The tetracyclic antidepressant mirtazapine is widely used in cancer patients suffering from anorexia. Although it is known to restore appetite, the exact mechanism remains unknown. The aim of the study was to evaluate if mirtazapine has any effect on gastric emptying in patients suffering from cancer-related anorexia. **Materials and Methods:** Solid-meal gastric-emptying study using radiolabeled meal was performed in 28 patients suffering from cancer anorexia once at baseline and repeated after 15 days of mirtazapine therapy. **Results:** At baseline, only 7 (25%) patients had normal gastric motility (emptying >70% at 3 h postingestion) whereas after treatment, 18 (64.2%) patients achieved this limit. Mean % gastric emptying increased from 55.2% ±21.0% to 68.9% ±21.3% ($P < 0.001$). Mean gastric emptying time ($t_{1/2}$) before intervention was 314.7 ± 421.0 min which decreased to 116.0 ± 106.7 min after intervention. Results were further analyzed by dividing the patients into two groups based on baseline gastric-emptying study. Group A (normal gastric emptying) consisted of seven patients, mean % gastric emptying at baseline and postintervention was 75.0% ±5.25% and 87.57% ±5.94%, respectively ($P < 0.018$). Group B (delayed gastric emptying) consisted of 21 patients, mean % gastric emptying at baseline and postintervention was 48.71% ±18.82% and 62.76% ±16.86%, respectively ($P < 0.001$). **Conclusion:** Mirtazapine significantly improves gastric emptying in patients of prostate and breast cancer suffering from cancer-associated anorexia.

Keywords: Cancer anorexia, gastric emptying, mirtazapine, technetium-99m-sulfur colloid

Introduction

Anorexia is defined as loss of desire to eat, resulting in reduced nutritional intake.[1] Anorexia is one of the most frequent complications of advanced malignancy, being present in up to 50% of cancer patients and results from derangement of the complex central and peripheral signaling pathways that control food intake.[2] Because of its complex origin, no specific therapy for cancer-related anorexia has been suggested. Most commonly used strategies are drug treatment, nutrition education strategies, and exercise strategies.[3]

Mirtazapine is a noradrenergic and specific serotonergic antidepressant and is known to promote appetite.[4] It has well-documented efficacy in managing symptoms of nausea and vomiting in the contexts of cancer chemotherapy and in perioperative settings.[5,6] The mechanism by which mirtazapine improves appetite is not completely understood and both central and peripheral actions have been proposed. Since gastric sluggishness is known to be prevalent in advanced cancer, it was postulated that mirtazapine possibly exerts the appetite-stimulating (orexic) property by normalizing or improving gastric emptying.[7] The aim of this study was to determine the effect of mirtazapine on gastric emptying on cancer patients suffering from anorexia.

Materials and Methods

Twenty-eight patients with cancer-associated anorexia were recruited in the study after informed consent. There were 19 males and 8 females in the group with a mean age of 60.85 ± 9.42 years, range 40–78 years. All the male patients have prostate as primary whereas all the female patients had breast cancer. They were put on 7.5 mg mirtazapine orally once a day. They underwent a radionuclide solid-meal gastric-emptying

Address for correspondence: Dr. Sukanta Barai, Department of Nuclear Medicine, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Rae Bareli Road, Lucknow - 226 014, Uttar Pradesh, India.
E-mail: danzig@rediffmail.com

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study at baseline and a follow-up gastric emptying study after 15 days while on mirtazapine. There were no obvious adverse effects and all patients could tolerate the drug and complete the study. Institute's Ethics Committee approved the study protocol.

Eligibility criteria for participants

Cancer patients complaining of anorexia for a minimum period of 2 weeks and not associated with any obvious reason were included in the study. Those patients who were unable to discontinue possible interfering drugs for 48 h before the study were excluded from the study. Patients with known autonomic neuropathy, gastroesophageal reflux disease, advanced renal failure, and hepatic failure were also excluded.

Patient preparation for gastric-emptying study

The patients were advised to report after overnight fasting after discontinuing medications those are likely to interfere in a gastric-emptying study like prokinetics 48 h prior. The patients were also advised about the logistical demands of the procedure (e.g., the meal to be used, the time required for eating the meal [10 min] and for imaging, the number of images required, and what the patient is allowed to do between images). Random blood sugar (RBS) was measured before study in each patient before baseline as well as follow-up study to rule out diabetes, patients with RBS >150 mg/dl were excluded from the study.

Radiolabeled meal was prepared by an experienced nuclear medicine technologist in a method standardized by Awasthi *et al*.[8] Freshly prepared 500 microcuries of technetium-99 m-sulfur colloid was mixed with wheat flour (50 g) and kneaded with 50–75 ml water. The dough was rolled into round breads and roasted on a heating pan. Along with radiolabeled breads, 50 g of cooked rice and 50 g of pigeon pea pulse with 100 ml of water were provided as meal to the patient. Total caloric value of food was 372.9 calories. The radiolabeled test meal was ingested as quickly as possible, optimally within 10 min. The time taken to ingest the meal was recorded and whether any portion of the meal was not eaten.

Gastric-emptying study

Gastric-emptying study was performed in accordance to the procedure laid down by the joint guideline of Society for Nuclear Medicine, American Neurogastroenterology and Motility Society.[9] On ingestion of the radiolabelled test meal, patients were positioned supine on a dual-head gamma camera. Dynamic images were obtained for 60 min in both anterior and posterior projection with a frame rate of one frame per minute in a 64 × 64 matrix using a general-purpose collimator. Subsequent delayed images were obtained in the same projections for 90 s at hourly intervals up to 3 h on the same camera as was used for the initial images. Postmirtazapine intervention, gastric-emptying studies were done under the identical conditions as the baseline study.

Interpretation criteria

Image interpretation was performed in accordance to the procedure laid down by the joint guideline of Society for Nuclear Medicine; American Neurogastroenterology and Motility Society.[9] Images were analyzed qualitatively as well as semiquantitatively; $t_{½}$ and percentage gastric emptying at 3 h were calculated for all the patients. If gastric emptying at 3 h was <70%, it was considered as delayed gastric emptying.

Statistical analysis

Categorical data were evaluated using Chi-square test while quantitative data were first checked for its normality; continuous data with normal distribution was assessed using paired *t*-test. Ordinal data and continuous data with asymmetric distributions were assessed using Wilcoxon signed-rank test. The confidence level of the study was kept at 95%; hence, a $P < 0.05$ indicated a statistically significant association. Data were analyzed using SPSS version 15.0 (SPSS Statistics for Windows, Version 15.0 is manufactured by Chicago: SPSS Inc.).

Results

At baseline, only 7 (25%) patients had normal gastric emptying, considering ≥70% emptying of radiolabeled meal at 3 h as cutoff whereas after treatment, 18 (64.2%) patients achieved this limit. Mean % gastric emptying increased from 55.2% ±21.0% to 68.9% ±21.3%, thus showing a significant improvement in percentage gastric emptying ($P \leq 0.001$). Mean gastric emptying time ($t_{1/2}$) before intervention was 314.7 ± 421.0 min which decreased to 116.0 ± 106.7 min after intervention.

Effect of mirtazapine was further analyzed by dividing the patients into two groups based on baseline percentage gastric emptying at 3 h, considering 70% emptying as cutoff. Group A (normal gastric emptying at baseline) consisted of seven patients, mean % gastric emptying at baseline and postintervention was 75.0% ±5.25% and 87.57% ±5.94%, respectively, $P \leq 0.018$. Gastric-emptying time at baseline and at postintervention study was 133.85 ± 36.02 min and 87.14 ± 13.76 min, respectively, $P \leq 0.019$.

Group B (delayed gastric emptying at baseline) consisted of 21 patients, mean % gastric emptying at baseline and postintervention was 48.71% ±18.82% and 62.76% ±16.86%, respectively, $P < 0.001$; gastric-emptying time at baseline and at postintervention study was 375.09 ± 485.80 min and 125.76 ± 57.52 min, respectively, $P < 0.001$. On initiation of mirtazapine therapy, 11 of 21 (52.3%) patients achieved a normal gastric emptying.

Discussion

The primary observation of this study is the ability of mirtazapine to improve gastric motility in patients suffering from cancer-associated anorexia. Gastroparesis is one of the most underdiagnosed problems in cancer patients and often overlooked as a potential etiology of anorexia and cancer cachexia. While the exact prevalence is not known, gastroparesis is common among patients with upper gastrointestinal tract and pancreatic malignancy.[10-13] Management options of gastroparesis in malignancy are limited as most of the patients with advanced malignancy are not ideal candidates for long-term erythromycin therapy or invasive management of gastroparesis.

Mirtazapine is a unique serotonergic 5-hydroxytryptamine 2/3 (5HT2/3) receptor antagonist and noradrenergic antidepressant, which has been used off-label for management of gastroparesis.[14] It blocks histamine H1 and serotonin 5-HT2A, 5-HT2C, and 5-HT3 receptors and stimulates 5-HT1A receptors in both peripheral and the central nervous system.[15] Stimulation of 5-HT1A receptors is believed to be responsible for its antidepressant and anxiolytic effects, whereas blockade of H1, 5-HT2A, and 5-HT2C receptors also contributes partly to some of its anxiolytic and sedative effects. Mirtazapine's impact on central neural systems involved in mood regulation could have partly contributed to its orexic property.[16] The mechanism of action of mirtazapine for gastroparesis is thought to be related to potent 5-HT3 antagonism and has been reported effective in relieving postoperative and recalcitrant severe gastroparesis.[17] The agonist effect of mirtazapine on 5-HT1A receptors also plays a role in improved gastric motility.[17] Gastric wall tone influences intragastric pressures and is partly responsible for the perception of satiety through increased afferent vagal activity. Receptive relaxation of gastric fundus region, a process predominantly controlled by the activity of nitrergic neurons, is known to be regulated by the stimulation of 5-HT1A receptors.[18] Improved gastric motility will allow for larger ingested volumes of liquid or solid food before satiety center is activated.

A review of literature did not reveal any study that has evaluated the effect of mirtazapine on gastric emptying in patients of cancer anorexia. There were few partly similar studies reporting effect of mirtazapine on anorexia and nausea and vomiting. In a preclinical animal study in 6 dogs, Yin *et al*. evaluated the effect of 45 mg mirtazapine administered 90 min before gastric-emptying study on gastrointestinal motility and reported that mirtazapine improves gastric emptying in healthy dogs and normalizes rectal distention-induced delay in gastric emptying and accelerates colon but not small intestinal transit in healthy dogs.[19] Kim *et al*. studied a case of recurrent postprandial discomfort, nausea, and vomiting resistant to conventional prokinetic agents and reported complete remission of recurrent postprandial discomfort, nausea, and vomiting within 1 week of starting of mirtazapine.[6] Riechelmann *et al*. treated 58 patients of cancer-related cachexia/anorexia with 15–30 mg mirtazapine orally every day and reported improvement of >1 kg weight and appetite in 25% patients after 8 weeks of therapy.[20] Thompson treated 19 of 20 gynecological or breast cancer patients (age from 36 to 74 years) with mirtazapine and reported a reduction in depressive symptoms, improved sleep continuity, decreased nausea, and improved appetite.[21]

There were few limitations in this study which could influence generalizability of the results. Number of participants was small (n = 28) with a male to female ratio of 2.3:1 and the participants belonged to prostate and breast cancer groups only.

Conclusion

Mirtazapine significantly improves gastric emptying in patients of prostate and breast cancer suffering from cancer-associated anorexia. The improvement in gastric emptying could partly be responsible for the appetite stimulating property of the drug. A prospective study with larger patient population with different type of primary malignancies should be conducted to define the precise role of mirtazapine in cancer-associated anorexia.

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Conflicts of interest

There are no conflicts of interest.

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