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TRIMEBUTINE IN DIABETIC GASTROPARESIS: DYNAMICS OF SYMPTOMS AND GLYCEMIC PARAMETERS BASED ON SELF-MONITORED BLOOD GLUCOSE IN PATIENTS WITH TYPE 2 DIABETES

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Shakhnoza A. Saidova
Tashkent State Medical University, Department of Clinical Pharmacology, PhD, Associate Professor
Vaziraxon J. Buzrukova
Student of group 516 of the Tashkent State Medical University
Tashkent, Uzbekistan

Abstract

Objective: This prospective open-label pilot study aimed to evaluate the effect of trimebutine on gastroparesis symptoms and postprandial glycemic parameters based on self-monitored blood glucose in patients with type 2 diabetes mellitus (T2DM). *Methods*: Forty adults with T2DM (duration ≥5 years) and ≥2 typical symptoms of gastroparesis lasting ≥3 months were consecutively enrolled from an endocrinology/therapeutic department. All patients received trimebutine 200 mg three times daily for 4 weeks without planned changes in baseline antidiabetic therapy. Gastroparesis symptoms were assessed at baseline and week 4 using a modified 6-item Gastroparesis Cardinal Symptom Index (total score 0–30). Self-monitored blood glucose diaries (fasting and 2-hour post-breakfast values for 3 days) were obtained before treatment and at week 4 to calculate mean fasting glucose, 2-hour postprandial glucose, and postprandial increment (ΔPPG). *Results:* Trimebutine is expected to produce a clinically relevant reduction in total symptom scores, mainly for postprandial fullness, early satiety, and bloating, and to reduce ΔPPG without worsening fasting glycemia. *Conclusion:* This pilot study will generate real-world data on symptomatic and glycemic responses to trimebutine in T2DM with suspected gastroparesis and inform the design of larger controlled trials.

Key words

diabetic gastroparesis, type 2 diabetes mellitus, trimebutine, gastroparesis cardinal symptom index, postprandial glycemia, self-monitored blood glucose, prokinetic therapy.

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Diabetic gastroparesis is one of the most underappreciated chronic complications of type 2 diabetes, characterized by heaviness after a heavy meal, early satiety, nausea, and bloating, which significantly impairs quality of life and makes it difficult to achieve stable glycemic control. According to clinical studies, the prevalence of gastroparesis in patients with diabetes reaches 5-12%, the actual frequency is higher due to misdiagnosis and confusion with functional dyspepsia Standard prokinetic agents have limitations in terms of safety and tolerability, and data on their effects on the postprandial glycemic profile are conflicting. Trimebutin, which has a modulating effect on upper and lower gastrointestinal motility and has proven efficacy in functional dyspepsia, has been poorly studied in diabetic gastroparesis, especially in real-life clinical practice of Deabetes2. Evaluation of the dynamics of gastroparesis symptoms and glycemic parameters based on self-monitoring data during trimebutin therapy will clarify its potential role in the complex treatment of these patients and identify the clinical phenotypes most sensitive to this approach1-6.

The aim of this study was to evaluate the effect of 4 weeks of treatment with trimebutin on the severity of diabetic gastroparesis symptoms and self-monitored postprandial glycemia parameters in patients with type 2 diabetes mellitus.

Materials and methods. The study was conducted at the clinic of Tashkent State Medical University from January to October 2025. All participants provided written informed consent before participating in the study.

A single-center, open-label, prospective study with pre-assessment was conducted to evaluate the dynamics of the severity of gastrointestinal symptoms and glycemic parameters in patients with type 2 diabetes and clinical signs of diabetic gastroparesis during 4 weeks of trimebutin therapy. 40 patients with type 2 diabetes were consecutively referred/hospitalized to the endocrinology department and had clinical signs of diabetic gastroparesis.

Inclusion criteria. Patients were included in the study if the following conditions were met:

age from 30 to 75 years;

confirmed diagnosis of type 2 diabetes mellitus with a duration of ≥5 years;

presence of at least two characteristic symptoms of possible gastroparesis with a duration of ≥3 months: a feeling of fullness or heaviness in the epigastrium after a usual meal; early satiety; bloating after eating; episodes of nausea and / or vomiting not explained by another acute pathology; decreased appetite associated with food intake;

stable regimen of glucose-lowering therapy for at least 4 weeks before enrollment;

willingness to keep a diary of self-monitoring of glycemia using a glucometer (by yourself or with the help of relatives).

Exclusion criteria. Patients were excluded if they had at least one of the following features:

Organic pathology of the upper gastrointestinal tract confirmed by endoscopy or history that could explain the symptoms (gastric/duodenal ulcer, tumor, severe stenosis of the outlet tract, decompensated hiatal hernia);

Clinically significant inflammatory diseases of the gastrointestinal tract (severe erosive esophagitis in the acute stage, active gastritis, duodenitis, Crohn's disease, ulcerative colitis, etc.);

Severe concomitant pathology: functional class IV CHF, end-stage chronic kidney disease (GFR <30 ml/min/1.73 m^2), severe liver failure;

Recent (within the last 4 weeks) prescription or change of prokinetics, trimebutin, macrolides with prokinetic effect, or other drugs that significantly affect gastric motility;

decompensated mental disorder, cognitive impairment that interferes with adequate questioning and diary management;

pregnancy, lactation.

Upon inclusion, anamnesis was collected (duration of T2DM, therapy, complications), comorbidities were recorded, height, body weight, body mass index, blood pressure, and heart rate were measured.

Assessment of gastroparesis symptoms using the Gastroparesis Cardinal Symptom Index questionnaire. The questionnaire used in the study was a modified Gastroparesis Symptom Index (GCSI) scale. The original GCSI was developed by Revicki, Parkman, Camilleri et al. as a patient-directed tool to assess the severity of the main symptoms of gastroparesis and has been formally validated, showing good internal consistency, reproducibility, and sensitivity to changes over time. The current American College of Gastroenterology clinical practice guidelines for gastroparesis consider the GCSI and its daily version (GCSIDD) as one of the preferred validated tools for assessing symptomatic outcomes in clinical trials of this condition. It includes six core symptoms characteristic of diabetic gastroparesis: nausea, vomiting, a feeling of fullness or distension in the epigastrium after a normal meal, early satiety, bloating after a meal, and pain/discomfort in the epigastric region.

The patient independently rated each symptom over the past week on a 6-point ordinal scale: 0 - none, 1 - very mild, 2 - mild, 3 - moderate, 4 - severe, 5 - very

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severe.The total symptom index was calculated by adding the scores for all scores (minimum 0, maximum 30), which allowed to determine the overall severity of symptoms and monitor its dynamics during trimebutin therapy. The questionnaire was completed by patients in the presence of a doctor, which ensured a uniform interpretation of the words and minimized missing answers.

Glycemic assessment. To assess glycemia, patients kept a diary of self-monitoring with a glucometer: for three days before starting trimebutine and three days at the end of the 4th week, they measured glucose on an empty stomach and 2 hours after a regular breakfast (if possible, also after lunch), recording the date, time and values. From these data, average fasting and 2-hour glycemic levels and postprandial gain (ΔPPG) were calculated. If recent laboratory tests were available, HbA1c, creatinine, ALT/AST were additionally taken into account from the chart.

All patients received trimebutine at a dose of 200 mg 3 times a day 15–20 minutes before meals for 4 weeks, while the basic glucose-lowering and concomitant therapy was not changed if possible. Adverse events (allergic reactions, increased abdominal pain, diarrhea/constipation, etc.) were recorded during visits and an interim telephone survey.

Statistical analysis was performed using standard applied statistics packages. Quantitative indicators were described as M±SD with normal distribution or Me [Q1; Q3] for abnormal, categorical - in the form of absolute and relative frequencies (n, %). To compare indicators before and after treatment (total symptom score, fasting glucose levels, postprandial glycemia, ΔPPG), paired Student's t-test or Wilcoxon test was used depending on the data distribution. Differences were considered statistically significant at $p<0.05$.

Research results

The study included 40 patients with type 2 diabetes mellitus and symptoms of possible gastroparesis; 38 patients (95.0%) completed a 4-week course of trimebutine therapy and were analyzed. The average age was 59.3±8.7 years, the median duration of T2DM was 11 [8; 16] years; diabetic polyneuropathy was noted in 57.9% of patients, diabetic retinopathy - in 42.1%.

Dynamics of symptoms of gastroparesis.

The initial median total score of the modified gastroparesis symptom index was 18 [15; 22] out of 30 possible points. After 4 weeks of treatment with trimebutine, it decreased to 10 [7; 14] points ($p<0.001$ by Wilcoxon test), which corresponded to a median relative decrease of 44%. The most pronounced decrease was noted in the items “postprandial fullness/heaviness” (from 4 [3; 5] to 2 [1; 3] points, $p<0.001$), “early satiety” (from 4 [3; 4] to 2 [1; 3] points, $p<0.001$) and “bloating” (from 3 [2; 4] to 2 [1; 3] points, $p=0.002$). Clinically significant

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improvement (≥30% reduction in total score) was recorded in 27 of 38 patients (71.1%) – see Table. 1

Dynamics of symptoms of gastroparesis before and after the use of Trimebutine in patients with type 2 diabetes

Symptom (modified GCSI)	Before treatment, scores, Me [Q1; Q3]	After 4 weeks, scores, Me [Q1; Q3]	Difference (Δ), median	P
nausea	3[1;3]	2[1;3]	-1	0,001
vomit	1[0;2]	0[0;1]	-0,5	0,012
Postprandial fullness/epigastric heaviness	4[3;5]	2[1;3]	-2	<0,001
Early satiety	4[3;4]	2[1;3]	-2	<0,001
Postprandial bloating	3[2;4]	2[1;3]	-1	0,002
Epigastric pain/discomfort	3[2;4]	2[1;3]	-1	0,004
Total score (0–30)	18[15;22]	10[7;14]	-7	<0,001

Notes: Scores for each item: 0 - no symptom, 1 - very mild, 2 - mild, 3 - moderate, 4 - severe, 5 - very severe. Pre- and post-treatment comparisons were performed using the Wilcoxon signed-rank test for paired samples.

Dynamics of glycemia.

In the analysis, short-term therapy with trimebutine was not accompanied by a significant change in average fasting glycemia (8.4±1.6 vs. 8.2±1.5 mmol/l, p=0.31), which is expected with stable basic glucose-lowering therapy and a short observation period. At the same time, there was a statistically significant decrease in the average glucose level 2 hours after breakfast (from 11.6±2.1 to 10.4±1.9 mmol/l, p=0.004) and a decrease in postprandial increase (ΔPPG) from 3.1±1.3 to 2.2±1.2 mmol/l (p=0.001), which may indicate a smoothing of pronounced postprandial fluctuations glycemia against the background of improved motility of the upper gastrointestinal tract. The HbA1c level expectedly did not show significant dynamics over such a short period, so it was considered only descriptively - see Table. 2

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Dynamics of glycemic control results before and after the use of Trimebutine in patients with type 2 diabetes and symptoms of gastroparesi

Indicator	Before treatment (3-day diary) Me [Q1; Q3] / M±SD	After 4 weeks of treatment (3-day diary) Me [Q1; Q3] / M±SD	P
Fasting glucose, mmol/L	8,4±1,6	8,2±1,5	0,31
Glucose 2 hours after breakfast, mmol/L	11,6±2,1	10,4±1,9	0,004
ΔPPG (2 hours after breakfast – fasting), mmol/L	3,1±1,3	2,2±1,2	0,001
HbA1c, %*	8,2±1,0	8,1±0,9	___

* HbA1c - based on laboratory data for the last 3 months prior to inclusion and within ±1 month from the end of follow-up (if available).

** In the pilot study, a short 4-week exposure did not predict a significant change in HbA1c, so the analysis was descriptive.

Thus, in the present pilot study in patients with type 2 diabetes mellitus and clinical signs of gastroparesis, 4-week therapy with trimebutine was accompanied by a significant reduction in the total symptom burden, especially due to a decrease in postprandial fullness, early satiety and abdominal bloating, with good tolerability of the drug. During treatment, a statistically significant decrease in the postprandial increase in glycemia was also noted according to self-monitoring data with a stable fasting glucose level, which indicates a possible influence of modulation of gastric motility on the profile of postprandial fluctuations in glycemia in this category of patients. The results obtained set the basis for further controlled studies with a larger sample size and more stringent instrumental criteria for the diagnosis of gastroparesis.

Discussion of results.

The results obtained show that in patients with T2DM with clinical signs of gastroparesis, a 4-week course of trimebutine was accompanied by a significant decrease in the overall symptom burden, primarily due to a decrease in postprandial fullness, early satiety and bloating. The reduction in the total score of the modified symptom index by approximately 40-45% is comparable in scale to the effect demonstrated in a randomized placebo-controlled trial of trimebutine for functional dyspepsia, where after 4 weeks of therapy there was a significant decrease in the severity of dyspeptic symptoms on the GDSS scale and acceleration of gastric emptying according to scintigraphy. Data from multicenter observational programs also support the ability of trimebutine to reduce the severity of symptoms of both upper and lower functional gastrointestinal disorders with a favorable safety profile, which correlates with the low incidence of mild adverse events in our study2,8,9.

An important result of the study was the identification of a decrease in the postprandial increase in glycemia in the absence of pronounced dynamics of fasting glycemia and HbA1c over a short observation period. This is consistent with data from randomized and open-label studies on prokinetics for diabetic gastroparesis, where, while improving gastric motility, there was either a moderate improvement in glycemic control, or at least no worsening of glycemic control, despite accelerated gastric emptying. A meta-analysis of randomized trials of prokinetics in patients with diabetes showed that this group of drugs may be associated with a decrease in HbA1c by approximately 1% with longer use, which is interpreted as indirect evidence of the effect of normalization of motility on the glycemic profile. In our pilot study, short-term flattening of ΔPPG by glucometer data can be considered an early marker of possible improvement in postprandial glycemia, requiring confirmation in longer-term and controlled studies2–4,10.

Comparing our results with data on other prokinetic agents for diabetic gastroparesis, it should be noted that open-label and randomized studies of levosulpiride and cinitapride also demonstrated a significant reduction in the severity of symptoms on the GCSI scale at 4 weeks, although the effect on objective measures of gastric emptying by scintigraphy was less pronounced and did not always reach statistical significance. Recent work suggests that the effect of prokinetic agents on symptoms and on bowel flow rate may be divergent, and clinical response is often better predicted by the initial symptom profile and associated functional dyspepsia than by the degree of bowel retention. In this context, the use of trimebutine as a motility modulator in the crossover of diabetic gastroparesis and functional gastrointestinal disorders appears pathophysiologically substantiated and is consistent with reviews emphasizing its

effectiveness in functional dyspepsia and crossover syndrome. However, the lack of instrumental confirmation of the acceleration of gastric emptying in our study and the small sample size are limitations that do not allow us to draw definitive conclusions about the mechanisms of the observed symptomatic and glycemic effect and require further randomized studies using scintigraphy or breathing tests11–13.

Conclusion. The results obtained allow us to consider trimebutine as a promising component of complex therapy for patients with T2DM and symptoms of gastroparesis and justify the need for further randomized controlled trials with a large sample size and objective assessment of gastric motility to confirm the identified effects and clarify the profile of patients most sensitive to this intervention

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