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Эффективность итоприда в терапии нарушения моторно-эвакуаторной функции желудка у больных сахарным диабетом 1 типа с автономной нейропатией

Буденная И.Ю., Глинкина И.В., Зилов А.В., Махов В.М., Мельниченко Г.А.

ГБОУ ВПО Первый МГМУ им. И.М. Сеченова, Москва
(ректор – член-корр. РАН В.П. Глыбочко)

Цель. *Изучить влияние терапии итопридом (Ганатон, Abbott) на гастроинтестинальные симптомы (ГИ) и моторно-эвакуаторную функцию (МЭФ) желудка у больных сахарным диабетом 1 типа (СД1) с нарушением МЭФ желудка и другими формами диабетической автономной нейропатии (ДАН).*

Материалы и методы. *34 пациента с СД1 с ДАН и нарушением МЭФ желудка были включены в открытое сравнительное параллельное проспективное рандомизированное исследование длительностью 6 недель: основная группа пациентов (17 чел.) получала итоприд в суммарной суточной дозе 150 мг, контрольная группа (17 чел.) препараты, влияющие на МЭФ желудка, не получала. Распространенность и выраженность ГИ оценивались методом анкетирования. МЭФ желудка исследовали с помощью изотопного дыхательного теста с использованием ^{13}С-октановой кислоты.*

Результаты. *В основной группе в результате терапии итопридом через 6 недель отмечено статистически значимое уменьшение времени эвакуации (T1/2) пищи из желудка: исходно медиана 89,0 [82,3; 101,0] мин. vs. 53,0 [45,0; 78,6] мин. (p<0,001); снижение встречаемости изжоги (p=0,013) и урежение симптомов кишечной диспепсии (p=0,005). В контрольной группе ни время эвакуации пищи, ни распространенность ГИ симптомов не изменились. Положительной динамики показателей углеводного обмена (гликемия натощак, постпрандиальная гликемия, фруктозамин), а также снижение частоты эпизодов гипогликемии во время теста ни в одной из групп не отмечено.*

Заключение. *У пациентов с СД1 с нарушением МЭФ желудка с ДАН терапия итопридом в суммарной суточной дозе 150 мг позволяет улучшить скорость эвакуации пищи из желудка. На фоне терапии итопридом отмечается снижение встречаемости изжоги и урежение симптомов кишечной диспепсиии, уменьшение выраженности клинических проявлений желудочной диспепсии. Улучшение МЭФ желудка не приводит к положительной динамике показателей углеводного обмена.*

Ключевые слова: *сахарный диабет; нарушение моторно-эвакуаторной функции желудка; гастроинтестинальные симптомы; дыхательный тест; итоприд*

Itopride hydrochloride efficacy in the management of delayed gastric emptying in type 1 diabetis mellitus patients in the presence of autonomic neuropathy

Budennaya I.Yu., Glinkina I.V., Zilov A.V., Makhov V.M., Melnichenko G.A.
Sechenov First Moscow State Medical University, Moscow, Russian Federation

Aim*. Evaluation of the itopride (Ganaton®, Abbot) therapy efficacy in the management of gastrointestinal (GI) symptoms and gastric motor function (GMF) in type 1 diabetis mellitus (T1DM) patients (pts) in the presence of GMF dysfunction and other forms of diabetic autonomic neuropathy (DAN).*

Materials and Methods. *The total of 34 patients with T1DM, GMF dysfunction and DAN were selected for randomized, prospective, open-label, comparative study. The duration of the study was 6 weeks. The study group (17 pts) received itopride 150 mg total daily. The control group (17 pts) did not receive any treatment for GMF. A questionnaire was used for the assessment of gastrointestinal (GI) symptoms. Gastric emptying velocity was evaluated with 13C-octanoate breath test.*

Results. *As a result of itopride therapy there was a statistically significant decrease in the amount of time (T1/2) needed for the gastric emptying. The median amount of time decreased from 89.0 [82.3; 101.0] min to 53.0 [82.3; 101.0] min (p<0.001); decrease of the incidents of gastroesophageal reflux (p=0.013) and symptoms of intestinal dyspepsia (p=0.005). In control group there was no change in parameters. There was no positive dynamics of glycaemic control parameters (fasting blood glucose, postprandial blood glucose, fructosamine), and no reduction in the frequency of hypoglycaemic episodes during the test in any of the groups.*

Conclusions. *Itopride therapy in T1DM patients with GMF dysfunction and DAN in the total daily dose of 150 mg improves gastric emptying velocity. This therapy also improves symptoms of gastroesophageal reflux and intestinal dyspepsia. Improvement GMF doesn't lead to positive dynamics of glycaemic control parameters.*

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Keywords: *diabetes mellitus; gastric motor function; gastrointestinal symptoms; breath test; itopride*

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Delayed gastric emptying (DGE) in type 1 diabetis mellitus (T1DM) patients as a form of gastrointestinal neuropathy remains poorly understood and underdiagnosed late complication.

Data on the prevalence of DGE in patients with T1DM are contradictory and vary from 20% to 65%, due to the survey of different groups of patients, as well as use of different diagnostic methods which vary in the amount of information. [1–6].

It was suggested that DGE does not affect life expectancy of T1DM patients [7], but is of practical importance due to GI symptoms and because of the potential impact on carbohydrate metabolism. Low gastric emptying velocity may lead to postprandial hypoglycaemia followed by hyperglycaemia which affects the development/progression of late complications of T1DM.

The high precision 99mTc gastric emptying scintigraphy is not widely used due to the need of radioactive source and it has to be conducted in specialized radiology department. The alternative method, ^{13}C-octanoate breath test (^{13}C is non-radioactive) can be used in clinical practice and is recognized as equivalent to scintigraphy [8–9]. The method sensitivity is 86%; specificity — 80% [10]. The test is safe since it uses stable non-radioactive isotope in small doses. This is the first time ^{13}C-octanoate breath test was used in the Russian Federation, at Endocrinology Research Centre(Moscow).

Since the main cause of clinical pathophysiology is disturbance of gastric motility, the use of prokinetics is appropriate for the therapy of DGE. Prokinetics are widely used in conservative gastroenterology practice for functional dyspepsia, gastroesophageal reflux disease, gallbladder dyskinesia. The need for long–term use of prokinetics created demand for a drug, which is free from side effects, characteristic for efficient prokinetic domperidon. In gastroenterology practice there is a well–proven prokinetic — itopride hydrochloride, Ganaton® (Abbot). Prokinetic itopride combines double mechanism of prokinetic action (blocking of D2–receptors and inhibition of acetylcholinesterase) with the absence of serious side effects typical for other prokinetics [12]. In particular, itopride does not prolong QT interval [13]. Furthermore, itopride ability to penetrate the blood–brain barrier is minimal. Itopride metabolism prevents undesirable drug interaction with drugs metabolized by cytochrome P450 enzymes [12].

Clinical studies have shown the efficacy of itopride for therapy of conditions associated with GI and DGE symptoms. It should be noted, that there are not enough reports on the use of itopride in patients with diabetes: Does itopride therapy improve quality of life, reduces the incidents and severity of GI symptoms due to DGE, as well to an improvement of the glycaemic control including reduction of the incidents of hypoglycaemia.

Aim

The main objective of the study was the evaluation of the itopride (Ganaton®, Abbot) therapy efficacy in the management of gastrointestinal (GI) symptoms and DGE in T1DM patients in the presence of DGE and other forms of diabetic autonomic neuropathy (DAN).

Materials and methods

The total of 34 patients over 18 years old with T1DM, abnormal DGE and DAN were selected for randomized, prospective, open-label, comparative study. The duration of the study was 6 weeks. This duration of study was chosen due to the fact that after 6 weeks it is possible to evaluate the effect of itopride therapy on DGE and GI symptoms.

The patients were randomly assigned to 2 groups: the study group (17 pts) received a daily dose of 150 mg of itopride (50 mg 3 times a day, 30 minute before meals); the control group (17 pts) did not receive any DGE medications. All participants of the study volunteered to participate in the examination as a part of the study and signed informed consent forms

The characteristics of the patients included in the study are presented in the Table 1.

To assess prevalence of GI sensations we used a valid questionnaire [3, 14–16]. For each question patients were asked to choose the appropriate score: 0 — symptom is absent; 2 — symptom is moderately expressed; 3 — symptom is strongly expressed. Total score of GI sensations was counted: 1–11 – mild, 12–22 – moderate, 23–33 – severe [3, 14–16].

To evaluate DGE ***^{13}C–octanoic acid breath test was used***. This test is based on the analysis of changes of ^{13}C/^{12}C ratio in the exhaled air after taking the drug labeled with ^{13}C [10].

Test technique [17]: before the test the patient exhales into the test tube. Later this breath sample will be used for comparison. Then patient receives a standard breakfast: 1 egg; 5 g butter; 2 slices of white bread; 200 ml of orange juice (318.5 kcal, 15.4 g protein, 15.8 g fat, 42.8 g carbohydrates) mixed with ^{13}C–octanoic acid (100 µl). Patient exhales into test tube every 15 min during next 4 hours.

Octanoic acid is not metabolized in the acid environment of the stomach. Upon entering the small intestine, octanoic acid is rapidly absorbed and later is subjected to cleavage and oxidation in liver. It results in production of ^{13}C–bicarbonate followed by increase in the proportion of ^{13}C in the exhaled carbon dioxide. The $^{13}CO_2$ breath content was measured by isotope ratio mass spectroscopy ($^{13}CO_2/^{12}CO_2$ "Heli-View", MediChem Ltd, South Korea) at Kurchatov Institute.

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Table 1

Patients' characteristics		
Parameter	Study group Itopride 150 mg /day (n=17)	Control group (n=17)
Male/Female, n [%]	6 [35]/11 [65]	9 [53]/8 [47]
Age, years (Me [25; 75]	34 [29; 40]	33 [25; 45]
DM1 duration, years (Me, [25, 75])	21 [15; 31]	25 [22; 40]
BMI, kg/m^2 (Me, [25, 75])	21,5 [20.3; 25.8]	22,5[20.4; 28.4]
Fasting glycemia, mmol/l (Me, [25,75])	9.6 [6.0; 12.8]	9,6 [7.0; 10.7]
HbA_{1c}, % (Me, [25, 75])	8.6[7.9; 9.6]	8.3[6.9; 9.2]
Fructosamine, μmol/l (Me, [25, 75])	296 [258.0; 329.0]	298 [266; 348.5]
GI symptom score total, (Me, [25, 75])	11[6; 16]	8[5.5; 14.5]
$T_{1/2}$, min (Me, [25, 75])	90.7 [83.0; 111.0]	90.5 [83.3; 107.6]
Retinopathy, n [%]	15 [88.2]	16 [94.1]
Nephropathy, n [%]	10 [58.8]	8 [47.1]
Peripheral neuropathy, n [%]	17 [100]	17 [100]

The delay in gastric emptying is measured by the pace of excretion of the isotope marker and total proportion of ^{13}C in the exhale sample in relation to its amount in the initial preparation. DGE is evaluated as follows: $T_{1/2}$ less than 75 min — normal; $T_{1/2}$ from 75 to 120 min — moderate delay; $T_{1/2}$ over 120 min — severe delay.

On the day of the breath test all patients has administered the usual dose of long-acting insulin. The prandial insulin dose was calculated based on the amount of carbohydrate units (CU) in the test standard breackfast (4 CU) and according to the patient's individual need in prandial insulin. Fasting glycaemia level was measured with glucose meter, then every 30 min during the breath test (4hours).

For all patients included in the study the pathology of the upper GI was ruled out with the endoscopy. Abdominal ultrasonography has been used to exclude patients with cholelithiasis. The patients taking drugs affecting DGE or abusing alcohol were also excluded from the study. Photometric nitroblue tetrazolium test was used for fructosamine level evaluation (the tests were performed at 'Hemotest' laboratory, using Olimpus AU2700 analyzer, Japan); normal range was established at 161–285 μmol/l.

Questionnaire for GI symptom assessment	
Symptom	Scale
Postprandial fullness	3 2 1
Early satiation	3 2 1
Upper abdominal pain	3 2 1
Upper abdominal discomfort	3 2 1
Nausea and/or vomiting	3 2 1
Bloating	3 2 1
Eructation	3 2 1
Heartburn	3 2 1
Acid regurgitation	3 2 1
Constipation and/or diarrhea, accompanied by a feeling of incomplete evacuation of bowel contents	3 2 1
Other_____	3 2 1
Total	|__|__|

Statistical analyses

Statistical data analyses were performed using SPSS/PASW statistics (Statistical Package for the Social Science/Predictive analysis software), version 13.0.

The Kolmogorov–Smirnov test was used to test the normality of the distribution. Descriptive statistics for interval scale indicators are presented as mean values and standard deviations. The ordinal scale indicators, or in a case of a distribution, significantly different from normal, are presented as median and quartiles (25th and 75th percentiles). Qualitative characteristics are presented as absolute frequencies and the proportion of the group as a percentage. The nonparametric Mann-Whitney U test was used to compare indicators that deviate from normal distribution and ordinal scale indicators. For nominal (categorical) dichotomous variables comparison the χ^2 (chi–square) criterion was used. For comparison of related quantitative indicators groups Wilcoxon test was used. Analysis of the correlation of two quantitative criterions was carried by the non-parametric Spearman rank correlation method. The indicator was considered statistically significant at $p < 0.05$.

Results and discussion

In the present study we found a positive effect of itopride therapy on DGE in patients with T1DM.

After 6 weeks of itopride therapy there was a statistically significant decrease in the amount of time needed for the evacuation of food from the stomach ($T_{1/2}$). In the control group the food evacuation time did not change. The results are presented on the Figure 1.

There was no difference between groups in number of patients who had recovered the gastric emptying velocity ($p = 0.161$) after 6 weeks. In the study group the recovery in the rate of food evacuation from the stomach was observed in 71% of patients (12 out of 17); and in control group it was observed in 47% of patients (8 out of 17). Among patients who received itopride therapy the improvement of gastric emptying velocity did not depend on the severity of DGE. In control group, the recovery of

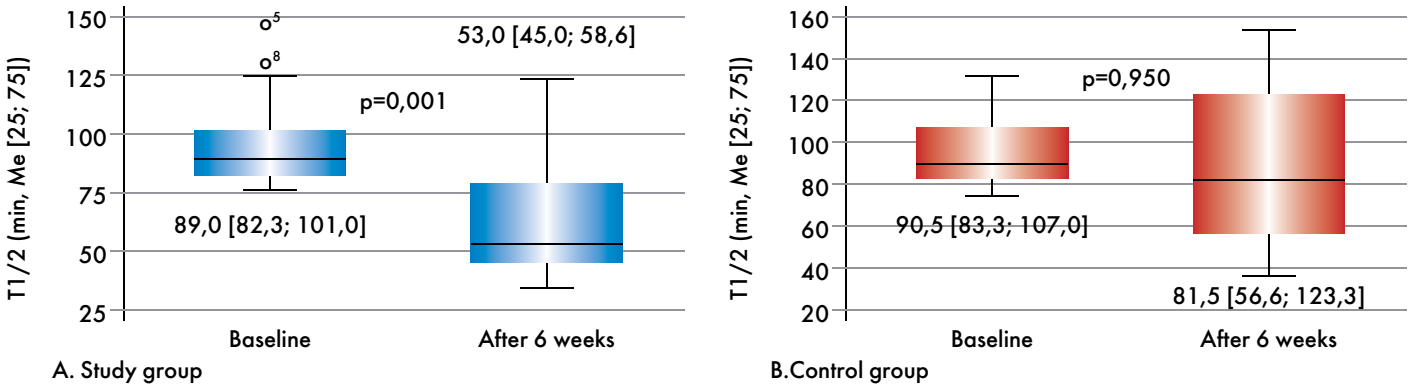

Figure 1. The impact of the itopride therapy on the gastric emptying velocity. Gastric emptying time (T1/2) with (A) and without (B) itopride therapy.

the gastric emptying velocity was observed only among patients who had negligible initial DGE: $T_{1/2}$ 75 to 80 min, which might be explained by the measurement error. For the rest of the patients (9 out of 17) the time of food evacuation either remained unchanged (4 out of 17), or became longer (5 out of 17). The findings suggest that itopride therapy is highly efficient in improving objective indicators of DGE in patients with T1DM.

The prevalence and severity of GI symptoms during itopride therapy

As can be seen from Figure 2, in the study group of patients it was observed a statistically significant reduction in the occurrences of GI symptoms after 6 weeks of therapy: heartburn ($\chi^2 = 6.103$; $p = 0.013$) and diarrhea/obstipation ($\chi^2 = 7.771$; $p = 0.005$). Based on the mechanism of action and published data on successful use of itopride therapy for the treatment of gastroesophageal reflux disease, we can assume that itopride has had a positive effect on the tonus of the lower esophageal sphincter. This, in turn, reduces the number of gastric reflux incidents and occurrences of heartburn.

The effect of itopride on such 'intestinal', i.e. caused by disturbance of intestinal motility, symptoms as diarrhea and obstipation, is most likely related to effect of the drug on the upper GI tract since it does not significantly affect intestinal motility. The reduction of the incidents of diarrhea and obstipation might be considered as a result of the itopride effect on the tonus and kinetic state of the biliary tract. The normalization of the gallbladder motility is usually results in the synchronization of excretion of bile into the duodenum. It optimizes the motility of small and lad large intestine and promotes the normalization of chemical and microbiological status of bowel. The reduction in the number of diarrhea and obstipation complaints during itopride therapy might be explained by normalization of such manifestation of DAN as DGE. The adequate evacuation of gastric contents into the small intestine is an important factor in maintaining intestinal motility. No statistically significant differences were found in the occurrence of other GI symptoms after prokinetic therapy as compared to the baseline.

Another result of the improvement of the velocity of the gastric emptying into duodenum is the decrease of the median score of GI symptoms: 11 [6; 16.5] baseline vs. 4 [3; 9] after therapy ($p = 0.011$), due to both a decrease in the prevalence and severity of GI symptoms. Thus, prior to itopride therapy half of the study group patients experienced moderate dyspepsia, after 6 weeks of itopride therapy no more than 25% of patients had GI symptoms.

In the control group there were no statiscally significant changes in incidence and severity of GI symptoms: median score 8 [5.5; 14.5] baseline vs. 8 [3.5; 12.5] 6 weeks later ($p = 0.552$).

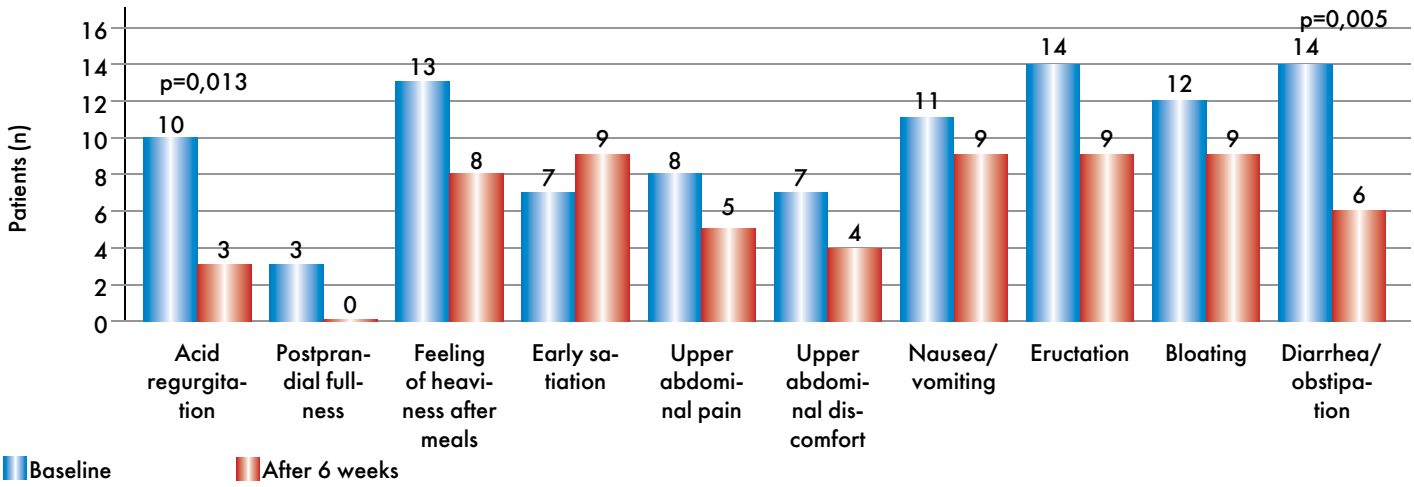

Figure 2.GI symptoms dynamics during itopride therapy (n = 17).

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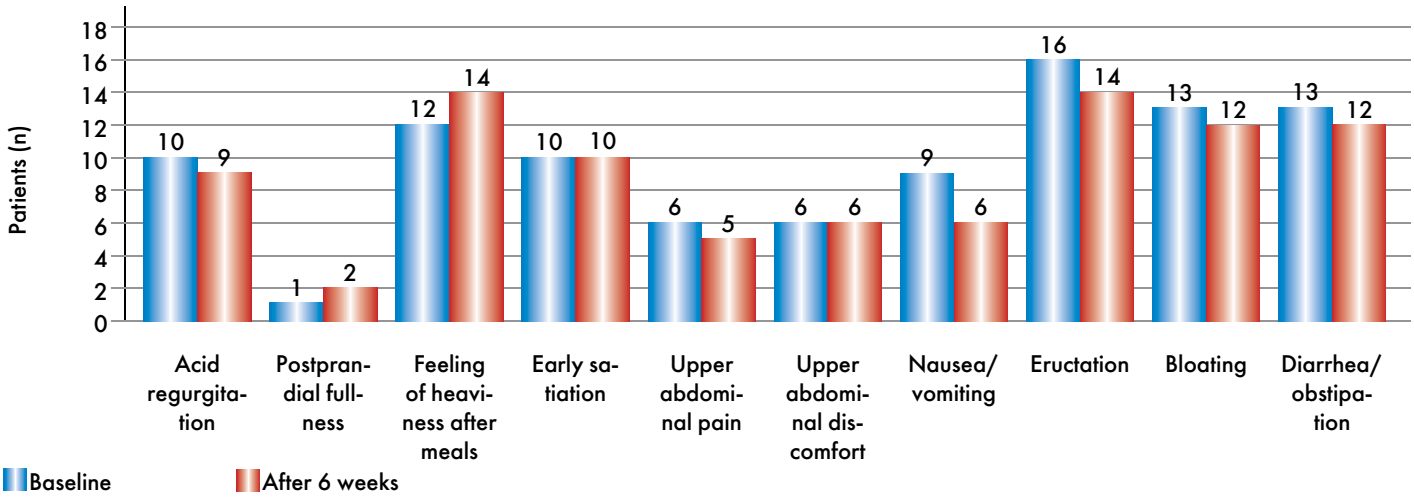

Figure 3. GI symptoms dynamics in control group (n = 17).

Table 2

Insulin dose dynamics in patients with DGE after 6 weeks, study and control groups (N1 = 17; N2 = 17, Me [25; 75] IU)

	Study group	Control group	p
Baseline insulin	20 [14.5; 25]	25 [17; 34]	0.683
Prandial insulin	25 [20; 32.5]	20 [18; 39]	0.839

Carbohydrate metabolism dynamics after 6 weeks of itopride therapy

The status of carbohydrate metabolism in both groups of patients was assessed by determining the fasting glycaemia level, postprandial glycaemia and fructosamine level. Fructosamine level was chosen as a parameter due to the duration of the study. Also, the frequency of hypoglycaemic episodes was assessed during the breath test.

There were no changes in drugs and insulin dose during the study (Table 2).

In assessing the impact of GI symptoms improvement during itopride therapy on carbohydrate metabolism we did not find positive dynamics neither in fructosamine level, nor in fasting and postprandial glucose levels (Table 3 and Figure 4).

Also, there were no reductions in hypoglycaemic episode frequency, despite DGE improvements (Table 3).

Prokinetic therapy is currently the for DGE treatment. Laway B.A. et al. demonstrated that as the goal parameters of carbohydrate metabolism are reached in patients with T2DM, the DGE symptoms is possible [18]. These results are most likely associated with transient impairments of DGE in patients with high blood glucose levels. In those patients who already have persistent DGE, it is possible to stabilize gastric motility with achievement and maintenance of target glycaemia level, but there is no improvement of GI symptoms parameters.

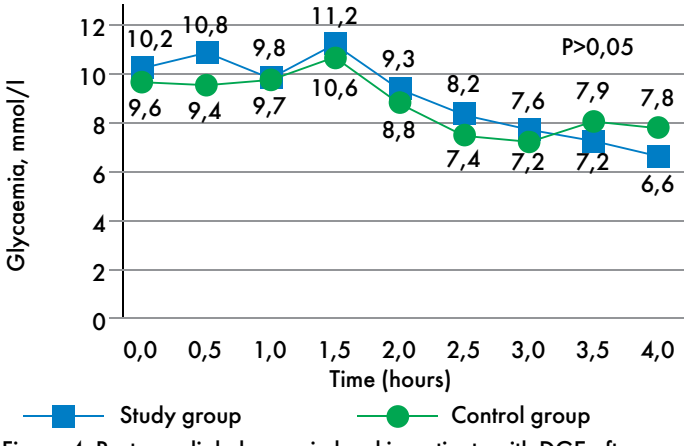

Figure 4. Postprandial glycaemia level in patients with DGE after 6 weeks in study and control groups (n1 = 17; n2 = 17; Me, μmol/l)

Conclusions

1. Itopride, in a dose of 150 mg daily for 6 weeks, tends to accelerate gastric emptying in T1DM with DGE.
2. Itopride improves clinical symptoms of DGE in T1DM.
3. Improvement of gastric emptying velocity does not result in positive carbohydrate metabolism dynamics.

Table 3

Glycaemic control in patients with T1DM and DGE after 6 weeks in study and control groups

	Study group Itopride 150 mg/day (n = 17)	Control group (n = 17)	p
T1/2, min (Me [25; 75])	53.0 [45.0; 58.6]	81.5 [56.6; 123.3]	0.031
Fructosamine, μmol/l (Me [25; 75])	280 [230; 320]	342 [268; 350]	0.084
Fasting glycaemia, mmol/l (Me [25; 75])	9.6 [6.0; 11,7]	10,2 [5.7; 13.7]	0.756
Episodes of postprandial hypoglycaemia, patients, n (%)	5 (29.4)	6 (35.3)	0.714

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Budennaya Irina Yur'evna	PhD student, Department of Endocrinology, I.M. Sechenov First Moscow State Medical University, Moscow, Russian Federation **Email: irina-budennaia@yandex.ru**
Glinkina Irina Vladimirovna	MD, PhD, Associate Professor, Department of Endocrinology, I.M. Sechenov First Moscow State Medical University, Moscow, Russian Federation
Zilov Aleksey Vadimovich	MD, PhD, Associate Professor, Department of Endocrinology, I.M. Sechenov First Moscow State Medical University, PhD of Medical Sciences, Professor, Gastroenterology Department, I.M. Sechenov First Moscow State Medical University, Moscow, Russian Federation
Mel'nichenko Galina Afanas'evna	MD, PhD, Academician at the Russian Academy of Medical Sciences, Professor, Department of Endocrinology, I.M. Sechenov First Moscow State Medical University; Endocrinology Research Centre, Moscow, Russian Federation