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The antidiabetic activity of the new composition "Thigliben" on the experimental dexamethasone diabetes mellitus model in rats

Being a metabolic disease with long-term hyperglycemia, diabetes mellitus significantly increases the risk of microvascular and macrovascular diseases and organ pathologies, respectively. The creation of the new composition "Thigliben", which allows not only qualitatively controlling diabetic hyperglycemia, but also providing a preventive and/or therapeutic effect on the development of diabetic polyneuropathy was pathogenetically reasonable.

Aim. To study the antidiabetic activity of "Thigliben" on the experimental dexamethasone diabetes mellitus in rats.

Materials and methods. The pharmacological study of the antidiabetic activity of the new composition "Thigliben" in the dose of 4 mg/kg was performed. The experimental studies were conducted on a standard model of the experimental dexamethasone type 2 diabetes mellitus in rats. Glibenclamide in the dose of 0.6 mg/kg (corresponds to an average human daily dose of 10 mg) was selected as the reference drug.

Results. It was found that by its effects on the carbohydrate and lipid metabolism the new composition "Thigliben" was similar to the reference drug glibenclamide administered in a higher dose. By the antioxidant activity this composition exceeded the effect of the reference drug, provided that normalization of the TBA-RS level in the liver homogenate was significant. The new composition "Thigliben" normalized all the parameters of the cerebral energy metabolism studied relative to the control pathology group and its efficiency was significantly higher than that of the reference drug glibenclamide. The new composition "Thigliben" increased the content of ATP by 109 % compared to the control pathology group, in contrast to 68 % on the background of glibenclamide; restored the activity of citrate synthase by 65 %, succinate dehydrogenase by 134 %, and pyruvate dehydrogenase by 61 % relative to the control pathology group. For glibenclamide the change in these indicators was 28 %, 50 %, and 22 %, respectively. The results obtained suggest that the metabolic effect of "Thigliben" composition is significantly more effective than that of the reference drug glibenclamide.

Conclusions. The new composition "Thigliben" is a promising antidiabetic drug with a pronounced hypolipidemic, antioxidant effect and the ability to restore energy deficiency; it is its significant advantage over the standard treatment regimens, including the average therapeutic doses of glibenclamide.

Key words: diabetes mellitus type 2; experimental pharmacology; complex hypoglycemic drugs; glibenclamide

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Антидіабетична активність нової композиції «Тіглібен» на моделі дексаметазонового цукрового діабету у щурів

Як метаболічне захворювання з тривалою гіперглікемією цукровий діабет значно збільшує ризик розвитку мікро- та макросудинних захворювань і відповідно органних патологій. Патогенетично виправданим було створення нового комплексного лікарського засобу «Тіглібен», що дозволяє не лише якісно контролювати діабетичну гіперглікемію, але й чинить профілактичну та/або лікувальну дію на розвиток діабетичної полінейропатії.

Мета дослідження. Вивчення антидіабетичної активності Тіглібену в умовах експериментального дексаметазонового цукрового діабету 2 типу у щурів.

Матеріали та методи. Проводилось фармакологічне вивчення антидіабетичної активності нової фармацевтичної композиції «Тіглібен» в дозі 4 мг/кг. Експериментальні дослідження проведені на стандартній моделі експериментального дексаметазонового цукрового діабету 2 типу у щурів. Препаратом порівняння був обраний глібенкламід у дозі 0,6 мг/кг (відповідає середньодобовій дозі для людини 10 мг).

Результати. Встановлено, що за впливом на вуглеводний і ліпідний обмін композиція Тіглібен знаходиться на рівні препарату порівняння глібенкламіду, що вводиться в більш високій дозі. За антиоксидантною активністю нова композиція перевищує дію референс-препарату, причому за нормалізацією рівня ТБК-АП в гомогенаті печінки достовірно. Також композиція Тіглібен нормалізувала всі досліджувані показники церебрального енергетичного обміну щодо групи контрольної патології і достовірно перевищувала ефективність препарату порівняння глібенкламіду. Композиція Тіглібен збільшувала вміст АТФ на 109 % щодо групи контрольної патології, на відміну від 68 % на тлі глібенкламіду; відновлювала активність цитратсинтази на 65 %, сукцинатдегідрогенази на 134 %, піруватдегідрогенази на 61 % щодо групи контрольної патології. Для глібенкламіду зміна цих показників склала 28 %, 50 % і 22 % відповідно. Отримані результати свідчать про те, що метаболічна дія композиції Тіглібен достовірно ефективніша, ніж препарат порівняння глібенкламід.

Висновки. Тіглібен є перспективним антидіабетичним лікарським засобом з вираженим гіполіпідемічним, антиоксидантним ефектом і здатністю відновлювати енергодефіцит, що є суттєвою перевагою нової композиції перед стандартними схемами лікування, що включають середньотерапевтичні дози глібенкламіду.

Ключові слова: цукровий діабет 2 типу; експериментальна фармакологія; комплексні цукрознижувальні препарати; глібенкламід

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Антидиабетическая активность новой композиции «Тиглибен» на модели дексаметазонового сахарного диабета у крыс

Как метаболическое заболевание с длительной гипергликемией сахарный диабет значительно увеличивает риск развития микро- и макрососудистых заболеваний и соответственно органных патологий. Патогенетически оправданным было создание нового комплексного лекарственного средства «Тиглибен», позволяющего не только качественно контролировать диабетическую гипергликемию, но и оказывающего профилактическое и/или лечебное действие на развитие диабетической полинейропатии.

Цель исследования. Изучение антидиабетической активности Тиглибена в условиях экспериментального дексаметазонового сахарного диабета 2 типа у крыс.

Материалы и методы. Проводилось фармакологическое изучение антидиабетической активности новой фармацевтической композиции «Тиглибен» в дозе 4 мг/кг. Экспериментальные исследования проведены на стандартной модели экспериментального дексаметазонового сахарного диабета 2 типа у крыс. Препаратом сравнения был выбран глибенкламид в дозе 0,6 мг/кг (соответствует среднесуточной дозе для человека 10 мг).

Результаты. Установлено, что по воздействию на углеводный и липидный обмен композиция Тиглибен находится на уровне препарата сравнения глибенкламида, вводимого в более высокой дозе. По антиоксидантной активности новая композиция превышает действие референс–препарата, причем по нормализации уровня ТБК-АП в гомогенате печени достоверно. Также композиция Тиглибен нормализовала все изучаемые показатели церебрального энергетического обмена относительно группы контрольной патологии и достоверно превышала эффективность препарата сравнения глибенкламида. Композиция Тиглибен увеличивала содержание АТФ на 109 % относительно группы контрольной патологии, в отличие от 68 % на фоне глибенкламида; восстанавливала активность цитратсинтазы на 65 %, сукцинатдегидрогеназы на 134 %, пируватдегидрогеназы на 61 % относительно группы контрольной патологии. Для глибенкламида изменение этих показателей составило 28 %, 50 % и 22 % соответственно. Полученные результаты свидетельствуют о том, что метаболическое действие композиции Тиглибен достоверно эффективнее, чем препарата сравнения глибенкламида.

Выводы. Тиглибен является перспективным антидиабетическим лекарственным средством с выраженным гиполипидемическим, антиоксидантным эффектом и способностью восстанавливать энергодефицит, что является существенным преимуществом новой композиции перед стандартными схемами лечения, включающими среднетерапевтические дозы глибенкламида.

Ключевые слова: сахарный диабет 2 типа; экспериментальная фармакология; комплексные сахароснижающие препараты; глибенкламид

Diabetes mellitus (DM) has become one of the most common diseases in the world, and according to the WHO, the proportion of adults with diabetes will be 69 % by 2030 [1]. Being a metabolic disease with long-term hyperglycemia, DM significantly increases the risk of microvascular and macrovascular diseases and organ pathologies, respectively [2]. Hyperglycemia at the macrovascular level induces and/or complicates the pathology of coronary arteries and cerebrovascular diseases, and in the case of disorders at the microvascular level mainly affects eyes, kidneys, and liver.

The creation of a new complex drug containing glibenclamide, thioctic acid and benfotiamine is pathogenetically reasonable [3]. The main mechanism of action of glibenclamide is the blockade of ATP-dependent potassium channels (K^+-ATP-channels), which are localized on the plasma membrane of pancreatic beta cells, it leads to depolarization of the membrane and the influx of Ca^{2+} ions through voltage-dependent calcium channels. An increase in the intracellular concentration of Ca^{2+} activates calcium / calmodulin-dependent proteinkinase II and stimulates exocytosis of secretory granules with insulin. Glibenclamide has the highest affinity for sulfonylurea receptors on beta cells and the most pronounced hypoglycemic effect among sulfonylurea preparations, and also has extra-pancreatic effects, such as increase in the sensitivity of peripheral tissues, primarily fatty and muscular ones, to insulin and improvement of the glucose uptake by cells. The hypoglycemic efficacy and the ability to prevent microvascular complications of glibenclamide were proven in such large studies as UKPDS, ADOPT [4]. The latter demonstrated a 2.2-fold reduction in the risk of cardiovascular complications in patients with type 2 diabetes mellitus on the background of glibenclamide administration.

Benfotiamine was introduced into the new composition in order to prevent the development and correction of diabetic polyneuropathy as it is able to level out the key changes in the structures of peripheral nerves and the microvasculature, which is typical for the pathogenesis of polyneuropathies. Benfotiamine normalizes metabolic processes in neurons, increases the transketolase activity, provides utilization of intermediate glycolysis products in the pentose phosphate cycle [5].

Thioctic acid (α-lipoic acid) is an endogenous antioxidant that participates in the mitochondrial energy production; it is characterized by a pronounced antitoxic effect, and demonstrates synergism with respect to insulin, which is due to the acceleration of glucose utilization. Thioctic acid is used in the treatment of diabetic polyneuropathy.

Thus, the development of a fixed combination of thioctic acid, glibenclamide and benfotiamine under a conditional name “Thigliben” will allow not

Table 1

Changes and weight gain in rats with dexamethasone diabetes mellitus (n=10)

No.	Group	Body weight, g		Changes in the body weight	p
		Day of the experiment			
		Day 1	Day 15		
1	Intact control	184 ± 2.50	196 ± 2.56	12.9 ± 0.91	–
2	Control pathology	186 ± 2.39	212 ± 2.31	27.6 ± 1.47	$p_{2-1}<0.001$
3	The composition containing glibenclamide (0.25 mg/kg) + thioctic acid (0.75 mg/kg) + benfotiamine (3 mg/kg)	184 ± 1.87	198 ± 1,83	16.4 ± 1.13	$p_{3-2}<0.001$
4	Glibenclamide (0.60 mg/kg)	185 ± 1.75	199 ± 2.50	15.7 ± 1.57	$P_{4-2}<0.001$

only qualitative control of diabetic hyperglycemia, but also a preventive and / or therapeutic effect on the development of diabetic polyneuropathy.

Previously, at the stage of screening studies, an effective dose of "Thigliben" composition was determined; it was 4 mg/kg. It consisted of glibenclamide – 0.25 mg/kg (corresponding to a human dose of 4.12 mg per day), thioctic acid – 0.75 mg/kg (corresponding to a human dose of 12.5 mg per day); benfotiamine – 3 mg/kg (corresponding to a human dose of 50 mg per day) [6].

The aim of our work was to study the antidiabetic activity of the new composition "Thigliben" on the main parameters of the carbohydrate and lipid metabolism, the system lipid peroxidation – antioxidant system (LPO-AOS), and the energy metabolism in the experimental diabetes mellitus type 2.

Materials and methods

Insulin-independent diabetes mellitus was modeled according to the recommendations by subcutaneous administration of dexamethasone glucocorticoid in rats in the dose of 0.125 mg/kg for 14 days with a simultaneous high-calorie carbohydrate diet [7].

The experimental animals were randomized into the following groups (10 rats per group): Intact control; Control pathology (14-day administration of dexamethasone + a high-carbohydrate diet); Animals that received the composition of glibenclamide in the dose of 0.25 mg/kg (corresponding to a human dose of 4.12 mg per day), thioctic acid in the dose of 0.75 mg/kg (corresponding to a human dose of 12.5 mg per day) and benfotiamine in the dose of 3 mg/kg (corresponding to a human dose of 50 mg per day) with under conditions of the experimental pathology; Animals receiving the reference drug glibenclamide in the dose of 0.60 mg/kg (corresponding to a human average daily dose of 10 mg) on the background of pathology.

For biochemical studies, animals were removed from the experiment (under ether anesthesia) on day 15, and the biomaterial was taken. The content of glucose, insulin, free fatty acids (FFA), triacylglycerols (TAG), cholesterol and high density lipoproteins (HDL) were determined using standard kits of firms "SpineLab", Ukraine; "Filisit-Diagnostics", Ukraine, "Lachema" Czech Republic. Thiobarbituric acid reagents (TBA-AP), reduced glutathione (G-SH), and catalase, which were determined by standard methods [8], were selected as indicators of the lipid peroxidation system – antioxidant system. To assess the participation of the new composition "Thigliben" in the energy metabolism, we studied the content of macroergic phosphates – ATP, ADP – in the brain tissues and the activity of citrate synthase, pyruvate dehydrogenase, and succinate dehydrogenase.

Animals were kept under standard conditions of the vivarium at the Central Research Laboratory of the NUPh. The studies were carried out in accordance with the National General Ethical Principles of Animal Experiments (Ukraine, 2001) based on the provisions of the European Convention for the Protection of Vertebrate Animals for Experimental and Other Scientific Purposes (Strasbourg, 1986). Statistical processing of the results was performed using AnalystSoft Inc. StatPlus and the Student criterion [9].

Results and discussion

It was found that by Day 15 of the experiment the significant changes in the body weight were recorded in animals (Tab. 1).

Animals of the control pathology group under conditions of the experimental insulin-independent diabetes mellitus demonstrated a significant increase in the body weight; the gain value was 2.15 times higher than in that of the intact control group.

The treatment-and-prophylactic administration of "Thigliben" composition allowed controlling changes in the body weight along with administration of dexamethasone and a high carbohydrate diet, the value of body weight gain was slightly higher than that in the group of rats treated with the reference drug glibenclamide in a higher average therapeutic dose. It should be noted that in the animals treated with "Thigliben" and glibenclamide the changes in

Table 2

The indicators of the carbohydrate and lipid metabolism in rats on the background of dexamethasone diabetes mellitus (n=10)

Intact control	Control pathology	The composition containing glibenclamide (0.25 mg/kg) + thioctic acid (0.75 mg/kg) + benfotiamine (3 mg/kg)	Glibenclamide (0.60 mg/kg)
Glucose, mmol/L (blood serum)			
5.17 ± 0.18	11.3 ± 0.32***	5.67 ± 0.17##	5.27 ± 0.15##
Insulin, pg/mL (blood serum)			
1,301 ± 22.5	2,076 ± 29.8***	1,472 ± 41.6##	1,394 ± 47.5##
FFA, mmol/L (blood serum)			
0.43 ± 0.04	0.83 ± 0.04***	0.61 ± 0.02**#	0.58 ± 0.03*##
TAG, mmol/L (blood serum)			
0.85 ± 0.05	1.91 ± 0.04***	1.01 ± 0.06##	0.91 ± 0.04##
Cholesterol, mmol/l (blood serum)			
2.19 ± 0.10	3.49 ± 0.11***	2.38 ± 0.09##	2.24 ± 0.10##
HDL, mmol/L (blood serum)			
1.18 ± 0.05	0.90 ± 0.03**	1.12 ± 0.04#	1.15 ± 0.04#
Glycosylated hemoglobin, % (blood serum)			
7.5 ± 0.5	9.6 ± 0.7*	8.6 ± 0.7*#	8.2 ± 0.5*#

Notes:
1) Statistically significant differences compared to the values of the intact control group * – $p<0.05$; ** – $p<0.01$; *** – $p<0.001$;
2) Statistically significant differences compared to the values of the control pathology group # – $p<0.01$; ## – $p<0.001$.

the body weight were at the level observed in the group of the intact control.

It is well known that administration of high doses of glucocorticosteroids may lead to a secretory dysfunction of pancreatic beta cells and development of insulin resistance. Dexamethasone diabetes mellitus in the experimental animals was verified by significant disturbances of the carbohydrate and lipid metabolism (Tab. 2).

A 2.1-fold increase in the glucose level in the control pathology group may be due to the fact that dexamethasone inhibits the expression of glucose transporters GLUT 1 and GLUT 4 [10, 11], and it causes a decrease in glucose utilization by peripheral tissues. At the same time, there is large-scale hyperinsulinemia as a compensatory reaction to hyperglycemia. The latter is indicative of the cell insensitivity to insulin and the development of severe insulin resistance (the insulin level in the control pathology group exceeds this indicator in the intact control group by 2.7 times).

In animals of the control pathology group dexamethasone diabetes mellitus and high-carbohydrate diet induced significant lipid metabolism disorders. By Day 15 of the experiment there was a significant increase in the concentration of free fatty acids (FFA) (by 197 %) and triacylglycerol (TAG) (by 228 %). The above is the result of the fact that due to the weakening of the inhibitory effect of insulin on the processes of lipolysis there is mobilization of fat from the adipose tissue, and the synthesis of atherogenic low-density lipoproteins and cholesterol by the liver increases. In addition, a decrease in the level of antiatherogenic high-density lipoproteins (HDL) was found, indicating an increase in their catabolism.

The increased content of FFA and TAG in the blood, their increased flow to the cells of organs and tissues provokes further disturbances of the cellular metabolism, increases hyperglycemia and hyperinsulinemia.

Administration of "Thigliben" normalized the parameters of carbohydrate and lipid metabolism studied to the limits of the physiological norm of the intact control, and was not inferior to the activity of the reference drug glibenclamide.

The pharmacological activity of "Thigliben" composition is explained by adding glibenclamide characterized by decreased concentration of glucose in the blood and the level of glycosylated hemoglobin to its content.

It should be noted that 58 % reduction in the dose of glibenclamide in the new composition did not lead to statistically significant differences in efficacy with the reference drug glibenclamide administered in the average daily dose by its effect on the carbohydrate and lipid metabolism. This phenomenon can be explained by potentiation of the activity of glibenclamide, benfotiamine and thioctic acid, which are components of "Thigliben".

Table 3

The indicators of the LPO-AOS system in rats on the background of dexamethasone diabetes mellitus (n=10)

Intact control	Control pathology	The composition containing glibenclamide (0.25 mg/kg) + thioctic acid (0.75 mg/kg) + benfotiamine (3 mg/kg)	Glibenclamide (0.60 mg/kg)
TBA-RS, μmol/L (blood serum)			
1.10 ± 0.05	2.93 ± 0.10***	1.86 ± 0.07***###$$	2.33 ± 0.04***##
TBA-RS, μmol/g (liver homogenate)			
80.9 ± 0.90	232 ± 9.07***	130 ± 4.84***##$	167 ± 5.12***##
G-SH, RU (liver homogenate)			
66.7 ± 1.38	30.6 ± 1.64***	57.9 ± 2.55*##	52.3 ± 1.19***##
Catalase, μkat/g (liver homogenate)			
0.39 ± 0.01	0.22 ± 0.02***	0.34 ± 0.01**#	0.31 ± 0.01***#

Notes:
1) Statistically significant differences compared to the values of the intact control group * – p<0.05; ** – p<0.01; *** – p<0.001;
2) Statistically significant differences compared to the values of the control pathology group # – p<0.01; ## – p<0.001;
3) Statistically significant differences compared to the values of the reference drug glibenclamide group $ – p<0.01; $$ – p<0.001.

The next stage of our work was to study the effect of "Thigliben" composition on the lipid peroxidation – antioxidant system (LPO-AOS) indexes in the experimental insulin-independent diabetes mellitus. The results are shown in Tab. 3.

One of the mechanisms of the toxic effect due to the excessive content of FFA in the blood is the activation of free radical oxidation. The results obtained show that in the control pathology group there is a significant prooxidant-antioxidant imbalance. The level of thiobarbituric acid reactive substances (TBA-RS) in the blood serum and the liver homogenate is 2.7-2.9 times higher than the values of intact control; it indicates a large-scale activation of lipid peroxidation. At the same time, there is a simultaneous decrease in the activity of the endogenous antioxidant system of the body; the level of G-SH in the liver homogenate is reduced by 54.3 %, and the activity of catalase by 46 %.

Administration of the new composition "Thigliben" significantly normalized the balance of AOS indexes to the level of intact control. In the mechanism of the antioxidant effect of "Thigliben" composition there is the activity recovery of both the nonenzymatic link of the AOS (an increase in the G-SH content by 89 % compared to the control pathology group) and the enzymatic level (an increase in the catalase activity by 60 % compared to the control pathology group).

By its ability to normalize peroxidation and restore the endogenous antioxidant system the new composition "Thigliben" is superior to the reference drug glibenclamide, provided that its effect on the level of TBA-RS in the liver homogenate is significant.

The advantages of the new composition "Thigliben" compared to the reference drug glibenclamide concerning the LPO-AOS imbalance recovery can be explained by the fact that the composition contains benfotiamine belonging to water-soluble biogenic bioantioxidants.

Thus, it was found that by its effects on the carbohydrate and lipid metabolism the new composition "Thigliben" was similar to the reference drug glibenclamide administered in a higher dose, and by the antioxidant activity this composition exceeded the effect of the reference drug, provided that normalization of the TBA-RS level in the liver homogenate was significant.

Diabetes mellitus is characterized by systemic metabolic disorders in addition to disorders of carbohydrate and lipid profiles, as well as LPO-AOS imbalance; disorders of the energy metabolism can be no less dangerous, leading to multiple complications and significantly aggravating the course of the disease.

The lack of energy in the cell leads to qualitatively similar metabolic and morphostructural disorders in various organs and tissues. Reduction of the energy production in mitochondria and development of numerous adverse biochemical changes lead to mitochondrial dysfunction and cause even more pronounced energy deficiency, irreversible damage, and cell death [12].

Brain cells are the most sensitive to energy deficiency. Taking into consideration the facts mentioned above it was deemed appropriate to study the parameters of the energy metabolism in brain cells on the background of the experimental dexamethasone diabetes mellitus and the possible

Table 4

The indicators of the energy metabolism in rats on the background of dexamethasone diabetes mellitus (n=10)

Intact control	Control pathology	The composition containing glibenclamide (0.25 mg/kg) + thioctic acid (0.75 mg/kg) + benfotiamine (3 mg/kg)	Glibenclamide (0.60 mg/kg)
ATP, μmol/g (brain homogenate)			
3.04 ± 0.06	1.27 ± 0.05***	2.64 ± 0.04******$	2.13 ± 0.05****###
ADP, μmol/g (brain homogenate)			
0.275 ± 0.005	0.335 ± 0.007***	0.276 ± 0.005###$	0.306 ± 0.005**#
Citrate synthase, nmol/min·per mg of protein (brain homogenate)			
4.81 ± 0.08	2.62 ± 0.07***	4.31 ± 0.08****###$	3.36 ± 0.15***##
Succinate dehydrogenase, nmol/min per·mg of protein (brain homogenate)			
7.45 ± 0.17	2.92 ± 0.10***	6.82 ± 0.13*###$	4.37 ± 0.20****###
Pyruvate dehydrogenase, nmol/min·per mg of protein (brain homogenate)			
29.9 ± 0.46	17.5 ± 0.47***	28.1 ± 0.57###$	21.3 ± 0.41****###

Notes:
1) Statistically significant differences compared to values of the intact control group * – p<0.05; ** – p<0.01; *** – p<0.001;
2) Statistically significant differences compared to the values of the control pathology group # – p<0.05; ## – p<0.01; ### – p<0.001;
3) Statistically significant differences compared to the values of the reference drug glibenclamide group $ – p<0.001.

impact of the new composition "Thigliben" on the energy metabolism.

The results of the study of the energy metabolism indicators on the background of insulin-independent diabetes are shown in Tab. 4.

In the control pathology group there was a significant 2.4-fold decrease in the ATP content compared to the intact control and a simultaneous 1.2-fold increase in ADP. It indicates the development of a large-scale energy deficiency in brain cells.

Disturbance of the enzymatic activity of energy processes was verified by a significant decrease in the activity of citrate synthase by 1.8 times, succinate dehydrogenase by 2.6 times, and pyruvate dehydrogenase by 1.7 times.

The new composition "Thigliben" normalized all the parameters of the cerebral energy metabolism studied relative to the control pathology group and its efficiency was significantly higher than that of the reference drug glibenclamide. The new composition "Thigliben" increased the content of ATP by 109 % compared to the control pathology group, in contrast to 68 % on the background of glibenclamide; restored the activity of citrate synthase by 65 %, succinate dehydrogenase by 134 %, and pyruvate dehydrogenase by 61 % relative to the control pathology group. For glibenclamide the change in these indicators was 28 %, 50 %, and 22 %, respectively. The results obtained suggest that the metabolic effect of "Thigliben" composition is significantly more effective than that of the reference drug glibenclamide.

A significant advantage of the new composition "Thigliben" compared to glibenclamide on the recovery of energy deficiency induced by insulin-independent DM is the introduction of benfotiamine into it.

After absorption, benfotiamin reaches the liver where with the help of thiamine phosphokinase it is phosphorylated to thiamine monophosphate, thiamine diphosphate, and thiamine triphosphate. The main active form is thiamine diphosphate or thiamine pyrophosphate. The latter is a part of at least four enzymes involved in the metabolism. Thiamine pyrophosphate is a part of pyruvate dehydrogenase and 2-oxo-ketoglutarate dehydrogenase complexes that catalyze the oxidative decarboxylation of pyruvic and α-ketoglutaric acids and, therefore, contribute to the release of energy from carbohydrates and amino acids. Transketolase, a thiamine-containing enzyme that provides the activity of non-oxidized form of the pentose phosphate cycle, is the major source of NADPH (H^+) and the only source of ribose-5-phosphate in cells [12].

Thus, benfotiamine is a direct participant in the processes of the energy metabolism; it explains the complete elimination of energy deficiency phenomena in animals receiving the new composition in the experimental diabetes mellitus.

The antioxidant therapy promotes improvement in DM compensation, normalization of glycemia since the activation degree of Nf-kB transcription factor in diabetes patients has a correlation dependency on the glucose control quality, the use of thioctic acid leading to suppression of oxidative stress and reduction of Nf-kB activation helps to eliminate hyperglycemia [12].

Thioctic (alpha-lipoic) acid plays an important role in providing the energy metabolism in the body,

prevents the development of metabolic acidosis and fatty liver dystrophy, promotes glucose oxidation, improves the processes of the energy formation and energy metabolism. Thioctic acid is a co-factor of the pyruvate dehydrogenase complex, and administration of thioctic acid in DM patients who have subclinical insufficiency of these enzymes leads to improved efficiency of the glucose use in both patients with an excessive and normal body weight.

Thioctic acid improves the glucose utilization by peripheral tissues, stimulating the glucose uptake, affecting the activation and translocation of GLUT-4 [10, 11].

The studies by A.E. Midaoui et al. (2003) have shown that thioctic acid is not only an antioxidant, but it also has the antihyperglycemic and antihypertensive effects; normalizing the formation of mitochondrial anion superoxide, it blocks the formation of glycation end products, and reduces insulin resistance.

Thus, the use of thioctic acid can be considered as aimed at the main pathogenetic mechanisms of oxidative stress, which is the central link in diabetes pathogenesis and its later complications.

CONCLUSIONS

1. The new composition "Thigliben" in the dose of 4 mg/kg (glibenclamide in the dose of 0.25 mg/kg, thioctic acid in the dose of 0.75 mg/kg, and benfotiamine in the dose of 3 mg/kg) under conditions of the experimental insulin-independent diabetes with a high carbohydrate load exhibits pronounced antidiabetic properties.

2. By the effect on the main parameters of the carbohydrate (glucose, insulin) and lipid (free fatty acids, triacylglycerols, cholesterol, high-density lipoproteins) metabolism the new composition is not inferior to the action of the reference drug glibenclamide in the dose of 0.60 mg/kg (corresponds to a human average daily dose of 10 mg), while the dose of the reference drug is almost 60 % higher than the dose of glibenclamide in the composition.

3. The new composition "Thigliben" has a marked antioxidant effect and reduces pathologic processes of LPO. The antioxidant activity of the new composition is superior to that of glibenclamide.

4. The experimental diabetes mellitus is accompanied by the development of a large-scale energy deficiency. The new composition "Thigliben" restores all the parameters of energy metabolism studied, and it is significantly more effective than the reference drug glibenclamide.

5. The new composition "Thigliben" is a promising antidiabetic agent with a pronounced antioxidant effect and the ability to restore cellular energy deficiency; it is a significant advantage of the new composition over standard treatment regimens, including the average therapeutic doses of glibenclamide.

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