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Substantiation of the choice of components for a combined drug used for the treatment of type 2 diabetes mellitus

Diabetes mellitus (DM) is one of the most common non-communicable diseases in the world. As evidenced by the UN resolution, DM is recognized as one of the most threatening diseases in the world. At present there are more than 382 million people with DM. In the EU almost 4-6 % of the population suffers from type 2 diabetes mellitus (DM 2). It should be noted that this disease occurs with an extremely high risk of complications, which lead to disability, morbidity and mortality of patients in this category.

Aim. To substantiate the choice of components for introduction of a combined drug used for the treatment of DM 2.

Materials and methods. The results of meta-analyses concerning medical information of the drug use when treating DM 2 were analyzed.

Results and discussion. The results of the comparative studies of antidiabetic drugs were generalized; the expediency and rationality of the use of metformin as a drug with the proven efficacy and safety when treating DM 2 was revealed.

Conclusions. The authors have proposed and substantiated the effectiveness of a new antidiabetic composition with two API: metformin (400 mg) and benfotiamine (20 mg). The new composition with metformin and benfotiamine has been confirmed by the pharmacological studies as a highly effective antidiabetic agent with a pronounced antioxidant effect and the ability to restore cellular energy deficiency.

***Key words**: combined antidiabetic drug; metformin; benfotiamine; algorithm of the primary development; pharmacological studies*

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Обґрунтування вибору компонентів комбінованого лікарського засобу для лікування ЦД2

Цукровий діабет (ЦД) є одним з найбільш поширених неінфекційних захворювань у світі. Як свідчить резолюція ООН, ЦД визнано однією з найбільш загрозливих хвороб у світі. На сьогодні зареєстровано понад 382 млн осіб, що хворіють на ЦД. У країнах ЄС майже 4-6 % населення страждають на ЦД 2 типу. Слід зауважити, що дане захворювання відзначається надзвичайно високим ризиком розвитку ускладнень, які призводять до втрати працездатності, інвалідизації та смертності хворих цієї категорії.

Метою роботи є обґрунтування вибору компонентів для впровадження нового комбінованого лікарського засобу для лікування ЦД2.

Матеріали та методи. Проаналізовані результати мета-аналізів стосовно медичної інформації застосування препаратів у лікуванні ЦД2.

Результати та їх обговорення. Узагальнені результати порівняльних досліджень гіпоглікемічних препаратів, виявлено доцільність та раціональність застосування метформіну як ЛЗ з доведеною ефективністю та безпекою у лікуванні ЦД2.

Висновки. Авторами запропонована та обґрунтована ефективність нової протидіабетичної композиції двох АФІ: метформіну (400 мг) і бенфотіаміну (20 мг). Нова композиція з включенням метформіну та бенфотіаміну підтверджена фармакологічними дослідженнями як високоефективний антидіабетичний засіб з вираженим антиоксидантним ефектом і здатністю відновлювати клітинний енергодефіцит.

***Ключові слова**: протидіабетичний комбінований лікарський засіб; метформін; бенфотіамін; алгоритм первинної розробки; фармакологічні дослідження*

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Обоснование выбора компонентов комбинированного лекарственного средства для лечения СД 2

Сахарный диабет (СД) является одним из наиболее распространенных неинфекционных заболеваний в мире. Как свидетельствует резолюция ООН, СД признан одной из самых угрожающих болезней в мире. На сегодня зарегистрировано более 382 млн человек, страдающих СД. В странах ЕС почти 4-6% населения страдают СД 2 типа. Следует отметить, что данное заболевание протекает с чрезвычайно высоким риском развития осложнений, которые приводят к потере трудоспособности, инвалидизации и смертности больных этой категории.

Целью работы было обоснование выбора компонентов для внедрения нового комбинированного лекарственного средства для лечения СД2.

Материалы и методы. Проанализированы результаты мета-анализов по медицинской информации применения препаратов в лечении СД2.

Результаты и их обсуждение. Обобщены результаты сравнительных исследований противодиабетических препаратов, выявлена целесообразность и рациональность применения метформина как ЛС с доказанной эффективностью и безопасностью в лечении СД 2.

Выводы. Авторами предложена и обоснована эффективность новой противодиабетической композиции двух АФИ: метформина (400 мг) и бенфотиамина (20 мг). Новая композиция с включением метформина и бенфотиамина подтверждена фармакологическими исследованиями как высокоэффективное антидиабетическое средство с выраженным антиоксидантным эффектом и способностью восстанавливать клеточный энергодефицит.

***Ключевые слова**: противодиабетическое комбинированное лекарственное средство; метформин; бенфотиамин; алгоритм первичной разработки; фармакологические исследования*

According to the State Statistics Service of Ukraine, diabetes mellitus (DM) ranks third in prevalence after cardiovascular diseases and cancer. Today 2.9 % of the country's total population (or 1 198 047 patients) have a confirmed diagnosis of diabetes; patients with type 2 diabetes (DM 2) are 90 % of them. Taking into account the high prevalence, the annual growth of the incidence and severe consequences of the disease the introduction of a new domestic combined drug for the treatment of DM 2 is of immediate interest.

The assessment of expediency and feasibility for creating drugs has shown that drugs for treating DM 2 have a wide target segment of the market and the target consumer. DM is the metabolic disorder of the multiple etiology characterized by chronic hyperglycemia with the impaired metabolism of carbohydrates, fats and proteins as a result of abnormalities in insulin secretion or the action of insulin [1-2]. The consequences of diabetes are long-term dysfunctions and failure of various organs. Since this disease is a multi-organ disease, i.e. involving many organs and systems of the body in the pathological process, and it is chronic, its therapy requires a comprehensive approach taking into account the main elements of the pathogenesis of the disease and minimizing associated complications [3].

The incidence of DM 2 increases with age. Additional risk factors associated with age are the presence of chronic pathological processes on the background of reduced compensation abilities of the body. All these facts require special attention to possible manifestations of adverse effects of drug therapy. One of the approaches for solving such problems is the adequate complex therapy, which main criteria are:

- decrease of the drug load on the body (for example, reducing the concentration of the API in a dosage form);
- the use of possibilities of systemic effects of one drug for simultaneous correction of the disturbed functions of several organs or systems;
- the use of additional therapy to prevent potential side and other negative effects.

Materials and Methods

The general scheme (algorithm) developed to create a combined drug on the basis of the known API consists of 5 stages: the assessment of expediency and feasibility for creating drugs; development of the profile for the future target product; development of the basic concept of the drug; the proof of the drug concept; optimization (correction) of the concept and the approval of the drug model [4].

An important source of information to determine the efficiency and safety of antihyperglycemic therapy is the results of the meta-analysis of large samples of medical information. Therefore, summarizing the results of comparative studies of hypoglycemic drugs, metformin is currently the drug with the most proven efficiency and safety for treating DM 2 [5-10].

Nowadays benfotiamine is considered to be the drug of the first choice for preventing the progression of neuropathy [11]. Numerous works of domestic and foreign researchers confirm the effectiveness of using drugs of benfotiamine for the treatment and prevention of diabetic polyneuropathy [12]. The experimental study by H. Hammes et al. demonstrates that benfotiamine blocks the basic mechanisms of the cellular pathology in hyperglycemia and prevents development of retinopathy [13]. When using benfotiamine it has been shown experimentally that there is a decrease of the oxidative stress in the cerebral cortex of the laboratory animals and the left ventricular myocardium, and improvement of the myocardial contractility [14].

Results and Discussion

Currently, there are several main categories of hypoglycemic drugs used for treating DM 2, they act on the different stages of the biochemical processes in the body and have different side effects (Tab. 1) [1, 15-17].

The optimal hypoglycemic drug must meet certain requirements:

- the effectiveness in reducing glucose levels in the blood;
- the minimal risk of hypoglycemia;
- the absence of cardiotoxicity, nephrotoxicity, hepatotoxicity;
- the ease of use.

Since 2005 metformin is the first-line drug of pharmacological intervention in DM 2 in the recommendations of the International Diabetes Federation (IDF), since 2006 it is the first-line drug together with non-pharmacological treatment of DM 2 within the framework of the recommendations of the American and the European Associations of diabetologists (ADA и EASD). Since 2007 metformin is the only drug in preventing development of DM 2 in the ADA recommendations [3; 18].

Table 1

Characteristics of the main categories of hypoglycemic drugs used for the treatment of DM 2

The drug category	The name of API	The effect on the pathogenesis of DM	Side effects and other disadvantages
Derivatives of sulfonyl-urea	Gliclazidum Gliquidone Glipizide Glimepiride Glibenclamide	Stimulation of the insulin secretion, increase of the sensitivity of insulin receptors	The risk of hypoglycemia, the weight gain
Meglitinides	Repaglinide Nateglinide	Stimulation of the insulin secretion	The risk of hypoglycemia, the weight gain
Biguanides	Metformin	Inhibition of glucose production by the liver, increase of the cell resistance to insulin. Decrease of the metabolic syndrome symptoms	Gastrointestinal side effects, lactic acidosis (in the presence of severe renal failure)
Thiazolidinediones	Pioglitazone Rosiglitazone	Selective activation of PPAR-gamma receptors, transcription modulation of genes sensitive to insulin involved in controlling the glucose level and lipid metabolism	Water retention, the weight gain. They can not be used in patients with heart failure
Alpha-glucosidase inhibitors	Acarbose Miglitol Guarem	Competitive inhibition of alpha-glucosidase. The slower absorption of certain carbohydrates in the GIT	Gastrointestinal side effects. The need for repeated administration throughout the day, the low potential for reducing glycosylated hemoglobin
Incretins: dipeptidyl peptidase-IV inhibitors (DPP-4)	Vildagliptin Sitagliptin	Increase of the glucose-dependent insulin secretion and decrease in the glucagon secretion	The increased risk of respiratory infections, high cost, insufficient experience of use

Metformin has a distinct "window of absorption", moreover, the absorption of metformin in the small intestine is saturating. It means that with the concentration increase of metformin in the intestinal lumen above a certain threshold level there is the absorption saturation [19]. Therefore, the absorption level of metformin from the gastrointestinal tract depends on the evacuation rate of metformin from the stomach. These features determine the complexity of developing tablets of metformin with sustained release that are suitable for taking once a day, and are now popular in research. These peculiarities of metformin pharmacokinetics suggest that a single administration of large doses of the drug (once a day) will be less effective than 2-3 times a day, but in the corresponding smaller doses. At the same time, smaller doses will help to reduce the side effects of the drug [19-20].

The effective daily dose of metformin is in the range from 1200 mg to 2000 mg according to the dose-effect curve [21]. The dose of metformin, in which gastrointestinal side effects are observed, is 400-500 mg. For further studies the variant of 400 mg multiple dose of metformin (1200 mg/day) was chosen. In our opinion, it appears to be the most optimal from the point of view of both effectiveness and reduction of side effects. A decrease in a single dose and, consequently, a single load on the body reduces the probability of side effects of the drug [19-20].

The possibility of developing the combination of an additional API with metformin for the corrective action on potential side effects of metformin and complications of DM 2 were analyzed. The progression of diabetes leads to development of late complications. In more than 50 % of DM 2 patients macro- and microvascular disorders are observed. Serious damages of nerve endings (neuropathy), capillaries (angiopathy), retino- and nephropathy are the main causes of disability and death in these patients [21-22].

Benfotiamine is an effective drug with a wide range of the therapeutic action; it can prevent development of diabetic polyneuropathy, retinopathy and nephropathy at the early stages, as well as progression of the disease, resulting in the possibility of using benfotiamine in the combined antidiabetic drug.

Thus, a new antidiabetic combination based on metformin and benfotiamine was substantiated. The composition consists of metformin – 72 mg/kg corresponding to the human daily dose of 1200 mg and benfotiamine – 3.6 mg/kg corresponding to the human daily dose of 60 mg. The new composition will allow to reduce side effects of metformin without changing its efficiency, as well as decrease the risk and severity of long-lasting complications of the disease due to the additional corrective treatment with benfotiamine.

In the course of further studies the pharmacological activity of the new composition based on metformin and benfotiamine was determined. The studies of the impact of the new composition based on metformin and benfotiamine on the main indicators of carbohydrate, lipid,

Table 2

Dynamics of the body weight growth in rats with dexamethasone-induced diabetes (n = 8)

No.	Group	The body weight, g		The dynamics of the body weight change	p
		The time of the experiment			
		1 day	15 days		
1	Intact control	182 ± 2.50	194 ± 2.56	11.9 ± 0.91	–
2	Control pathology	184 ± 2.39	210 ± 2.31	25.6 ± 1.47	$p_{2-1} < 0.001$
3	The composition of metformin (72 mg/kg) + benfotiamine (3.6 mg/kg)	182 ± 1.87	196 ± 1.83	14.4 ± 1.13	$p_{3-2} < 0.001$
4	Metformin (90 mg/kg)	183 ± 1.75	197 ± 2.50	13.7 ± 1.57	$P_{4-2} < 0.001$

and energy metabolism, as well as decrease the lipid peroxidation – antioxidant system (LPO-AO system) were performed under conditions of the experimental DM 2. According to the recommendations, insulin-independent diabetes was modeled by a subcutaneous injection of glucocorticoid dexamethasone in the dose of 0.125 mg/kg in rats for 14 days with the simultaneous keeping of animals on the high-calorie hydrocarbon diet [23].

In the study 4 groups of animals were used: intact control; control pathology; animals received the composition of metformin in the dose of 72 mg/kg (corresponding to the human average daily dose of 1200 mg) and benfotiamine in the dose of 3.6 mg/kg (corresponding to the human daily dose of 60 mg) on the background of the experimental pathology; animals received the reference drug metformin in the dose of 90 mg/kg (corresponding to the human average daily dose of 1500 mg) on the background of the experimental pathology (Tab. 2-5).

The studies have shown that the new composition in the conditions of insulin-independent diabetes with a high carbohydrate load shows a pronounced antidiabetic activity. Decrease in the daily dose by 20 % (1200 mg/day vs 1500 mg/day) did not lead to statistically significant deviations in the effectiveness of the antidiabetic action.

By the effect on the main indicators of 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 refe-

Table 3

Indicators of the carbohydrate and lipid metabolism in rats on the background of dexamethasone-induced diabetes (n = 8)

Intact control	Control pathology	The composition of metformin (72 mg/kg) + benfotiamine (3.6 mg/kg)	Metformin (90 mg/kg)
Glucose, mmol/L (blood serum)			
5.15 ± 0.18	11.1 ± 0.32*	5.65 ± 0.17**	5.25 ± 0.15**
Insulin, pg/ml (blood serum)			
1299 ± 22.5	2074 ± 29.8*	1470 ± 41.6**	1392 ± 47.5**
Free fatty acids (FFA), mmol/L (blood serum)			
0.41 ± 0.04	0.81 ± 0.04*	0.59 ± 0.02*/**	0.56 ± 0.03*/**
Triacylglycerols (TAG), mmol/L (blood serum)			
0.83 ± 0.05	1.89 ± 0.04*	0.99 ± 0.06**	0.89 ± 0.04**
Cholesterol, mmol/L (blood serum)			
2.17 ± 0.10	3.47 ± 0.11*	2.36 ± 0.09**	2.22 ± 0.10**
High density lipoproteins (HDL), mmol/L (blood serum)			
1.16 ± 0.05	0.88 ± 0.03*	1.10 ± 0.04**	1.13 ± 0.04**

Notes: * – significant deviation of the indicator compared to the intact control group, $p < 0.01$; ** – significant deviation of the indicator compared to the control pathology group, $p < 0.01$.

Table 4

Indicators of the LPO-AO system metabolism in rats on the background of dexamethasone-induced diabetes (n = 8)

Intact control	Control pathology	The composition of metformin (72 mg/kg) + benfotiamine (3.6 mg/kg)	Metformin (90 mg/kg)
TBA-AP, mcmol/L (blood serum)			
1.08 ± 0.05	2.91 ± 0.10*	1.84 ± 0.07 */**/***	2.31 ± 0.04*/**
TBA-AP, mcmol/g (liver homogenate)			
80.7 ± 0.90	230 ± 9.07*	128 ± 4.84 */**/***	165 ± 5.12*/**
G-SH, c.u. (liver homogenate)			
66.5 ± 1.38	30.4 ± 1.64*	57.7 ± 2.55*/**	52.1 ± 1.19*/**
Catalase, μkat/g (liver homogenate)			
0.37 ± 0.01	0.20 ± 0.02*	0.32 ± 0.01*/**	0.29 ± 0.01*/**

Notes: * – significant deviation of the indicator compared to the intact control group, $p < 0.01$; ** – significant deviation of the indicator compared to the control pathology group, $p < 0.01$; *** – significant deviation of the indicator compared to the group that received metformin, $p < 0.01$.

Table 5

Indicators of the energy metabolism in rats on the background of dexamethasone-induced diabetes (n = 8)

Intact control	Control pathology	The composition of metformin (72 mg/kg) + benfotiamine (3.6 mg/kg)	Metformin (90 mg/kg)
ATP, mcmol/g (brain homogenate)			
3.02 ± 0.06	1.25 ± 0.05*	2.62 ± 0.04*/**/***	2.11 ± 0.05*/**
ADP, mcmol/g (brain homogenate)			
0.273 ± 0.005	0.333 ± 0.007*	0.274 ± 0.005**/***	0.304 ± 0.005*/**
Citrate synthase, nmol/min,·mg of protein (brain homogenate)			
4.79 ± 0.08	2.60 ± 0.07*	4.29 ± 0.08*/**/***	3.34 ± 0.15*/**
Succinate dehydrogenase nmol/min,·mg of protein (brain homogenate)			
7.43 ± 0.17	2.90 ± 0.10*	6.80 ± 0.13*/**/***	4.35 ± 0.20*/**
Piruvate dehydrogenase nmol/min, mg of protein (brain homogenate)			
29.6 ± 0.46	17.3 ± 0.47*	27.9 ± 0.57**/***	21.1 ± 0.41*/**

Notes: * – significant deviation of the indicator compared to the intact control group, $p < 0.01$; ** – significant deviation of the indicator compared to the control pathology group, $p < 0.01$; *** – significant deviation of the indicator compared to the group that received metformin, $p < 0.01$.

rence drug metformin in the dose of 90 mg/kg (corresponding to the human average daily dose of 1500 mg), moreover, the dose of the reference drug is 20% higher than the dose of metformin included in the composition.

CONCLUSIONS

The new composition with metformin and benfotiamine has a pronounced antioxidant action, restores all parameters of the energy metabolism studied (ATP, ADP, citrate synthase, succinate dehydrogenase, piruvate dehydrogenase); moreover, it significantly exceeds the efficiency of the reference drug metformin in the dose of 90 mg/kg.

The new composition with metformin (72 mg/kg corresponding to the human daily dose of 1200 mg) and benfotiamine (3.6 mg/kg corresponding to the human daily dose of 60 mg) has been confirmed by the pharmacological studies as a highly effective antidiabetic agent with a pronounced antioxidant effect and the ability to restore cellular energy deficiency. This composition has a significant advantage compared to the standard treatment regimens that include average therapeutic doses of metformin.

Conflicts of Interest: authors have no conflict of interest to declare.

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