STUDY OF HYPOGLYCEMIC PROPERTIES OF «GLYPHASONORM» TABLETS AND «GLYPHASOLIN» CAPSULES ON THE STREPTOZOTOCIN-INDUCED DIABETIC RAT MODEL

Viktoriia Rybak, Alexander Honcharov, Viktoriia Korol

The risk of developing any complications of diabetes is significantly reduced by monitoring and correcting blood glucose levels and blood pressure, as well as by observing healthy lifestyle rules. Early detection and treatment of type 2 diabetes contribute to the prevention of disease progression and the development of complications. The aim is to study the hypoglycemic effect of «Glyphasonorm» tablets and «Glyphasolin» capsules in a rat model of streptozotocin-induced diabetes.

Materials and methods. The studies were carried out on Wistar rats injected intraperitoneally with nicotinamide at a dose of 230 mg/kg 15 minutes before intravenous injection of streptozotocin at a dose of 65 mg/kg. The dynamics of body weight of rats, glucose and glycosylated haemoglobin levels under the impact of long-term administration of metformin, «Glyphasonorm» tablets and «Glyphasolin» capsules were investigated.

Results and discussion. The studies on a streptozotocin-induced diabetic model have established that under the action of «Glyphasonorm» tablets and «Glyphasolin» capsules, the level of glycosylated haemoglobin, which decreased along with the level of glucose in the blood of animals, was significantly reduced in comparison with diabetic control. After 14 days of research, the «Glyphasolin» capsules showed more pronounced hypoglycemic activity (4.4 % and 8.0 % more) than the «Glyphasonorm» tablets and the reference drug metformin. The «Glyphasolin» capsules on the 12th day of the study showed a marked decrease in glycosylated haemoglobin in the blood of animals (3.1 % and 5.6 % more) than the «Glyphasonorm» tablets and metformin.

Conclusions. In the experimental model of streptozotocin diabetes in rats, “Gliphasolin” capsules showed a more pronounced hypoglycemic effect, which was manifested by a decrease in the content of glycosylated haemoglobin in the blood and prevailed over the effect of the comparative drug metformin and “Gliphasonorm” tablets.

«Glyphasolin» capsules and «Glyphasonorm» tablets based on bioflavonoid complex from bean show promise in the treatment of type 2 diabetes on the background of obesity and reducing the risk of micro- and macroangiopathy.

Keywords: streptozotocin-induced diabetes, hypoglycemic activity, glycosylated haemoglobin, metformin, «Glyphasonorm» tablets, «Glyphasolin» capsules


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1. Introduction

Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Chronic hyperglycemia in DM is accompanied by damage, dysfunction, or failure of various organs and systems, including the eyes, kidneys, nervous system, heart, and blood vessels [1, 2]. The results of studies based on the principles of evidence-based medicine indicate that chronic hyperglycemia in DM is accompanied by damage, dysfunction or insufficiency of various organs and systems, including the eyes, kidneys, nervous system, heart and blood vessels – a high risk of developing cardiovascular diseases (CVD) [1, 3].

The risk of developing any complications is significantly reduced by controlling and correspondingly correcting the level of glucose in the blood and blood pressure, as well as following the rules of a healthy diet and performing regular physical exercises. Early detection and treatment of DM type 2 help to prevent the progression of the disease and the development of complications [4, 5].

The updated 2021 American Diabetes Association (ADA) guidelines present glycemic control goals for most patients with type 2 DM. Unfortunately, glycemic control goals are far from glycemic reality: every 8th patient with DM has an HbA1c >10.0 %, every 5th–>9.0 %, and every 2nd–>8.0 %. In general, 64.2 % of patients with DM type 2 in the world are in a state of decompensation.

In connection with the high toxicity and ability to cumulate synthetic hypoglycemic drugs, research on the study of biologically active substances of medicinal plants of the Fabaceae family – common bean (Phaseolus vulgaris L.) and golden bean (Phaseolus aureus L.). It has been proven that a thick extract from beans, which includes phenolic compounds represented by flavonols, isoflavones, isoflavonanes, isoflavans, pterocarps, oxycinnamic acids, coumarins and amino acids [5] in ED₅₀
During the modelling of experimental type 2 DM, the possible risk of animal death due to the cytotoxic effect of streptozotocin on pancreatic β-cells was taken into account.

After the reproduction of the experimental model of type 2 DM, starting from the second day of the experiment, the comparison drug and experimental drugs were used in the treatment.

In the dynamics of the experiment, according to methodological recommendations, changes in indicators of the hypoglycemic activity of drugs were studied, such as the level of glucose and glycosylated haemoglobin in the blood of animals and body weight.

The evaluation of the effect of tablets “Glyphasonorm” and capsules “Glyphasolin” was carried out in the middle of the group and between groups, taking into account their characteristics and in comparison with the diabetic control, the comparison drug metformin, using statistical analysis of the study results.

3. Materials and methods

Experimental research is a fragment of the research work of the National University of Pharmacy, approved by the Ministry of Health of Ukraine: “Pharmacological study of biologically active substances and medicinal products” (state registration number 0114UU000956).

Experimental studies were conducted in accordance with the requirements of the bioethics commission of the National Academy of Sciences of Ukraine (protocol No. 5 dated 15.01.2019) and the “General ethical principles of animal experiments”, which correspond to the provisions of the “European Convention on the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes” (Strasbourg, 1985) [8].

Non-linear white male rats were bred in the vivarium of the Central Scientific Research Laboratory of the National Academy of Sciences and were kept on a standard diet in accordance with sanitary and hygienic requirements.

Nicotinamide was administered intraperitoneally at a dose of 230 mg/kg body weight of rats 15 minutes before intravenous injection of streptozotocin at a dose of 65 mg/kg, which resulted in moderate and stable hyperglycemia and 40 % preservation of pancreatic insulin reserves [9].

When studying hypoglycemic activity, all animals were divided into 5 groups (10 in each). Animals of groups 1 and 2 (intact control and diabetic control) intragastrically received an equivalent amount of drinking water, group 3 – the comparison drug metformin, group 4 – tablets “Glyphasonorm” and group 5 – capsules “Glyphasolin”.

The study of the effect of “Glyphasonorm” tablets, “Glyphasolin” capsules and the comparison drug – metformin on the level of glycosylated haemoglobin (HbA1c) was carried out on 4 groups of animals (10 in each). Animals of group 1 (diabetic control) intragastrically received an equivalent amount of drinking water, group 2 – metformin, group 3 – tablets “Glyphasonorm” and group 4 – capsules “Glyphasolin”.

The proposed experimental model of streptozotocin diabetes with simultaneous administration of nicotinamide is due to the partial protection of pancreatic β-cells from the cytotoxic effect of streptozotocin with the help of appropriate doses of nicotinamide. Thus, this model allows you to reproduce the main pathogenetic signs of type 2 DM in humans, namely, impaired insulin secretion and action, and has certain advantages for studying the hypoglycemic effect of new drugs with different mechanisms of action.

During the planning of the experiment, such characteristics of animals as age, sex, and body weight were considered for the formation of experimental groups.
Starting from the second day of the study, animals with experimental streptozotocin diabetes were injected orally (twice a day) for two weeks with the comparison drug metformin at a dose of 50 mg/kg, tablets “Glyphasonorm” and capsules “Glyphasolin” at a dose of 40 mg/kg.

Metformin (diaformin, tab. 0.5 g), manufactured by JSC “Farmak”, Ukraine, was chosen as a reference drug. The choice of the comparison drug is due to the fact that metformin is a standard hypoglycemic drug, which is included in the treatment standards for DM of both types [10]. The therapeutic dose of metformin for rats was calculated from the daily dose for humans using the species sensitivity coefficients of Y. P. Rybolovlev [11].

The effect of metformin, “Glyphasonorm” tablets and “Glyphasolin” capsules on the body weight dynamics of animals with experimental streptozotocin diabetes was studied after 3 and 14 days of the study and this indicator was evaluated in comparison with the initial body weight of each animal.

The hypoglycemic activity of “Glyphasonorm” tablets and “Glyphasolin” capsules were studied in comparison with metformin in the model of streptozotocin diabetes with long-term administration (after 3, 5, 7, 10, 12 and 14 days).

As indicators of carbohydrate metabolism, the concentration of glucose (glucose oxidase method using a set of reagents from the company “Filisit-Diagnostika”, Ukraine) and HbA1c (hemoglobin cyanide method using a set of reagents “Agat-Med”, Russia) were determined in the blood serum of animals [12].

The glucose oxidase method (Drabkin method) is based on the reaction of its oxidation in the presence of the enzyme glucose oxidase with the formation of hydrogen peroxide, which in turn oxidizes orthotolidine in the presence of peroxidase to form coloured products. Glucose concentration was judged by the number of coloured products.

The haemoglobin cyanide method consists of the interconnection of Hb with ferric blue potassium, which is oxidized to methemoglobin, forming haemoglobin cyanide. The HbA1c content was estimated by the intensity of haemoglobin cyanide staining [13].

Statistical analysis of the results was performed using the standard package of the STATISTICA 6.0 program. Statistically significant differences between groups in the case of multiple comparisons were determined by Student’s test with Bonferroni correction.

4. Research results

The general condition of the animals in the experimental and control groups was assessed by the dynamics of body weight. After 3 days of the study, after simulating streptozotocin diabetes, body weight decreased in all groups of animals. In the group of diabetic control animals, body weight decreased by 10.7 %, in the treatment of which metformin was used – by 7.4 %, “Glyphasonorm” tablets – by 6.6 %, and “Glyphasolin” capsules – by 4.7 % in comparison with initial data (Table 1).

On the 14th day of the study, the greatest loss of body weight was observed in the group of diabetic control animals (by 24.0 %) compared to the initial data. At the same time, a 14.4 % decrease in body weight was recorded in the group of animals receiving metformin and in the groups of animals receiving “Glyphasonorm” tablets – by 11.5 % and “Glyphasolin” capsules – by 7.9 % compared to the initial data, which indicates a more active behaviour of the animals than in the diabetic control group.

No statistically significant differences were found between the comparison drug metformin and the studied drugs (Table 1).

The effect of “Glyphasonorm” tablets and “Glyphasolin” capsules on the body weight dynamics of rats in the streptozotocin diabetes model with long-term administration, (X ± Sx), (n=10)

<table>
<thead>
<tr>
<th>Research object, mg/kg</th>
<th>Dynamics of body weight (g)</th>
<th>In 3 days</th>
<th>In 14 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic control</td>
<td>Output data</td>
<td>In 3 days</td>
<td>In 14 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin (50 mg/kg)</td>
<td>240.0±1.29</td>
<td>222.3±2.74</td>
<td>205.5±2.52</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>«Glyphasonorm» tablets (40 mg/kg)</td>
<td>225.3±3.47</td>
<td>210.5±3.11</td>
<td>199.5±1.89</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p&lt;0.05</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>«Glyphasolin» capsules (40 mg/kg)</td>
<td>235.0±1.29</td>
<td>224.0±3.32</td>
<td>216.5±3.58</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>

Note: p – the significance of changes compared to the original data.

It is believed that the primary disorder in type 2 DM and impaired glucose tolerance is a decrease in the sensitivity of peripheral tissues to insulin, and the deterioration of β-cell function occurs secondarily as a mechanism aimed at compensating for insulin resistance [2].

The level of glucose in the blood is an integral indicator of the compensation of carbohydrate metabolism. Therefore, the state of glycemia was evaluated dynamically during the entire experiment. The research results showed that 3 days after simulating streptozotocin diabetes, a sharp increase in basal hyperglycemia (12.65±0.02) was observed in the rats of the diabetic control group, and after 5 days and before the end of the experiment, a slight decrease in the blood glucose level (8.86±0.04) (Table 2)

At the same time (at the height of the development of non-insulin-dependent diabetes), a high level of glucose was recorded in the blood of animals treated with metformin (10.05±0.06 mmol/l), “Glyphasonorm” tablets (11.75±0.04 mmol/l) and “Glyphasolin” capsules (11.45±0.07 mmol/l) in comparison with the initial data.

After 5 days of using “Glyphasolin” capsules and “Glyphasonorm” tablets in the treatment of diabetic animals, a slight decrease in the level of glucose in the blood was established – by 17.6 % and 15.0 %, compared to when metformin was used in the treatment of animals – by 23.1 % in comparison with the indicators of animals of the diabetic control group.

After 7 and 10 days of research, capsules “Glyphasolin” contributed to a significant reduction in the level of
glucose in the blood of animals (by 30.8 % and by 31.1 %) than metformin (by 28.4 % and by 27.7 %), and tablets “Glyphasonorm” reduced the level of glucose in the blood of animals by 27.2 % and by 28.5 % in comparison with the indicators of animals in the diabetic control group.

The hypoglycemic activity of “Glyphasolin” capsules after 12 and 14 days of the study was 43.5 % and 58.2 %, which is 6.5 % and 8.0 % higher than the hypoglycemic activity of metformin. The more pronounced hypoglycemic activity of tablets and capsules based on thick bean extract than the comparison drug metformin is due to the presence in its composition of various classes of natural compounds represented by flavonols, isoflavones, isoflavanones, isoflavans, pterocarpans, oxycinamic acids, coumarins and amino acids. Beans contain derivatives of guanidine, which are bases and act according to the type of biguains, and in the composition of a thick extract than the comparison drug metformin contributes to lowering the level of glucose in the blood of animals but did not normalize it to baseline values. “Glyphasolin” capsules showed more pronounced hypoglycemic activity than “Glyphasonorm” tablets and the comparison drug metformin.

Thus, “Glyphasolin”, “Glyphasonorm” tablets and metformin contributed to lowering the level of glucose in the blood of animals but did not normalize it to baseline values. “Glyphasolin” capsules showed more pronounced hypoglycemic activity than “Glyphasonorm” tablets and the comparison drug metformin.

It is known that among biochemical indicators, the HbA1c level can be a standard for evaluating the effectiveness of the hypoglycemic effect of the drug, as it represents the average level of glycaemia over three months. HbA1c is formed during a non-enzymatic reaction from haemoglobin and blood glucose (Maillard reaction). An increase in the level of blood glucose in DM significantly accelerates this reaction, which leads to an increase in the level of HbA1c in the blood. Since the lifetime of erythrocytes is, on average, 120 days, the level of HbA1c indicates the average level of glycaemia during three months [14, 15].

An HbA1c level in the range of 5.7 % – 6.4 % is characteristic of prediabetes, and a level of 6.5 % or higher is a manifestation of DM. When the level of HbA1c increases by 1 %, the risk of developing cardiovascular diseases increases by 10 % [16, 17].

Throughout the study, the level of HbA1c in the group of diabetic control animals remained elevated (7.4±0.02 μmol/l – 7.18±0.08 μmol/l) (Table 3), as well as the level of glucose in the blood (12.65±0.02 mmol/l – 8.86±0.04 mmol/l) (Table 2).

In animals treated with metformin, “Glyphasonorm” tablets and “Glyphasolin” capsules, with hyperglycemia at 10.05±0.06 mmol/l; 11.75±0.04 mmol/l and 11.45±0.07 mmol/l (Table 2), after 3 days of the study there was an increase in HbA1c at the level of 6.02±0.03 μmol/l; 6.51±0.03 μmol/l and 6.31±0.08 μmol/l (Table 3), which is a reference to the value of compensated DM [13].

After 5 days of research in the groups of animals treated with metformin, capsules “Glyphasolin” and tablets “Glyphasonorm”, there was a significant decrease in the level of HbA1c by 24.2 %, by 23.6 % and by 21.9 % in comparison with the indicators of diabetic control, but its high blood level still persisted.

After 7 days of research and treatment of animals with “Glyphasolin” capsules, the highest reduction of HbA1c by 39.6 % was recorded. Under the influence of metformin, the level of HbA1c decreased by 35.7 %, and under the influence of Glyphasolin tablets – by 33.6 % compared to the diabetic control.

Since, at the same time, “Glyphasolin” capsules showed a more pronounced hypoglycemic effect and an advantage over metformin and “Glyphasonorm” tablets, this can be seen in the reduction of the HbA1c level, which is directly proportional to the average concentration of glucose in the blood of animals.

It was established that after 14 days of research, “Glyphasolin” capsules reliably reduced the concentration of HbA1c in the blood of animals by 34.1 %, “Glyphasonorm” tablets by 32.2 % and were not inferior to metformin, under the influence of which the level of HbA1c in the blood decreased by 30.9 % (p<0.05) in comparison with the indicators of animals with control pathology, which is directly proportional to the average concentration of glucose in the blood of animals. At the same time, an active decrease in the glucose level in the blood of animals under the influence of “Glyphasolin” capsules by 36.8 %, “Glyphasonorm” tablets by 35.0 % and metformin by 33.4 % were determined.

### Table 2

Hypoglycemic activity of “Glyphasonorm” tablets and “Glyphasolin” capsules on the streptozotocin diabetes model in rats with long-term administration, (x ± Sx), (n=10)

<table>
<thead>
<tr>
<th>Research object/ mg/kg</th>
<th>Output data</th>
<th>Dynamics of glucose content (C, mmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>In 3 days</td>
<td>In 5 days</td>
</tr>
<tr>
<td>Intact control</td>
<td>4.49±0.08</td>
<td>4.40±0.02</td>
</tr>
<tr>
<td>Diabetic control</td>
<td>4.32±0.05</td>
<td>12.65±0.02</td>
</tr>
<tr>
<td>Metformin (50 mg/kg)</td>
<td>4.40±0.03</td>
<td>10.05±0.06*</td>
</tr>
<tr>
<td>«Glyphasonorm» tablets</td>
<td>4.51±0.02</td>
<td>11.75±0.04*</td>
</tr>
<tr>
<td>(40 mg/kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>«Glyphasolin» capsules</td>
<td>4.38±0.03</td>
<td>11.45±0.07*</td>
</tr>
<tr>
<td>(40 mg/kg)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: * – p<0.001 – the significance of changes compared to the “diabetic control” group; ** – p < 0.001 – the significance of changes compared to the “Metformin” group; *** – p<0.05 – the significance of changes compared to the “Metformin” group.
The effect of “Glyphasonorm” tablets and “Glyphasolin” capsules on the level of glycosylated haemoglobin (HbA1c) in the rat model of streptozotocin diabetes with long-term administration, (x±S), (n=10)

<table>
<thead>
<tr>
<th>Research object, mg/kg</th>
<th>Dynamics of HbA1c content (C, μmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>In 3 days</td>
</tr>
<tr>
<td>Diabetic control</td>
<td>7.44±0.02</td>
</tr>
<tr>
<td>Metformin (50 mg/kg)</td>
<td>6.02±0.03*</td>
</tr>
<tr>
<td>“Glyphasonorm” tablets (40 mg/kg)</td>
<td>6.51±0.03*</td>
</tr>
<tr>
<td>“Glyphasolin” capsules (40 mg/kg)</td>
<td>6.31±0.08*</td>
</tr>
</tbody>
</table>

Note: * – р<0.001 – the significance of changes compared to the “Diabetic control” group; ** – р<0.05 – the significance of changes compared to the “Metformin” group.

After 10 and 12 days of the study, there was an active reduction of HbA1c under the influence of “Glyphasolin” capsules by 36.2 % and 43.8 %, “Glyphasonorm” tablets by 34.1 % and 40.7 %, metformin by 32.2 % and by 38.2 % compared to the diabetic control.

After 14 days of treatment of animals with metformin, “Glyphasolin” capsules and “Glyphasonorm” tablets, HbA1c was not detected in the blood of the animals (Table 3) since, at this time, there was an active decrease in the level of glucose in the blood of the animals of the experimental groups by 50.2 %, by 58.2 % and 53.8 % (Table 2).

The research results showed that the greatest effectiveness in reducing the level of HbA1c was found during the treatment of animals with experimental streptozotocin diabetes, “Glyphasolin” capsules by 38.2 % and 43.8 %, “Glyphasonorm” tablets by 34.1 % and 40.7 %, metformin by 32.2 % and by 38.2 % compared to the diabetic control.

During the treatment of animals with “Glyphasolin” capsules, “Glyphasonorm” tablets, or metformin, under the influence of which the level of HbA1c in the blood decreased by 30.9 % compared to the initial data, tablets “Glyphasonorm” at a dose of 40 mg/kg reduced the body weight of animals by 11.5 % (р<0.001), and metformin at a dose of 50 mg/kg – by 14.4 % (р<0.001) compared to the initial data [19].

The hypoglycemic activity of “Glyphasolin” capsules at the end of the study was 36.8 %, which is 3.4 % higher than the hypoglycemic activity of metformin. “Glyphasonorm” tablets showed less hypoglycemic activity (by 1.8 %) than “Glyphasolin” capsules and more (by 1.6 %) than the comparison drug metformin. It should be noted that in animals that received “Glyphasolin” capsules, “Glyphasonorm” tablets, or metformin, the level of glucose in the blood did not normalize [19].

It was established that after 14 days of research, “Glyphasolin” capsules reliably reduced the concentration of HbA1c in the blood of animals by 34.1 %, “Glyphasonorm” tablets by 32.2 % and were not inferior to metformin, under the influence of which the level of HbA1c in the blood decreased by 30.9 % (р<0.05) in comparison with the indicators of animals with control pathology, which is directly proportional to the average concentration of glucose in the blood of animals. At the same time, an active decrease in the level of glucose in the blood of animals under the influence of “Glyphasolin” capsules by 36.8 %, “Glyphasonorm” tablets by 35.0 % and metformin by 33.4 % were determined [20].

The obtained results are an experimental justification for the use of “Glyphasonorm” tablets and “Glyphasolin” capsules for the complex treatment of DM of mild and moderate severity, as well as with a tendency to obesity. “Glyphasolin” capsules are planned to be introduced at PJSC “Khimpharmzavod “Chervona Zirka”” (Ukraine).

Study limitations. In the conditions of the conducted research, there was a limitation related to the individual non-tolerance (species sensitivity) of specific doses of nicotinamide and streptozotocin by experimental animals during the modelling of type 2 streptozotocin diabetes to study the hypoglycemic properties of “Glyphasonorm” tablets and “Glyphasolin” capsules.

Prospects for further research. The duration and quality of life of patients with DM are currently...
6. Conclusions

1. Tablets “Glyphasonorm” and capsules “Glyphasolin” in an experimental model of streptozotocin diabetes probably reduced the level of glycosylated haemoglobin, which decreased together with the level of glucose in the blood of animals compared to diabetic controls.

2. After 14 days of research, “Glyphasolin” capsules showed more pronounced hypoglycemic activity than “Glyphasonorm” tablets and the comparison drug metformin (by 4.4 % and 8.0 %, respectively).

3. Under the influence of “Glyphasolin” capsules, on the 12th day of the study, a more pronounced decrease in glycosylated haemoglobin in the blood of animals was established than in the case of “Glyphasonorm” tablets and metformin (by 3.1 % and 5.6 %, respectively).

4. Capsules “Glyphasolin” and tablets “Glyphasonorm” based on a bioflavonoid complex with beans are promising in the therapy of DM type 2 against the background of obesity and reducing the risk of developing micro- and macroangiopathy.

Conflict of interests

The authors declare that they have no conflict of interest in relation to this research, including financial, personal, authorship or other nature, which could affect the research and its results presented in this article.

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