PharmacologyOnLine
Archives • 2021 • vol.2 • 1310-1316

«KORVITIN®» - NEW THERAPEUTIC OPPORTUNITIES

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Abstract

Korvitin® is an original water-soluble complex of quercetin with polyvinylpyrrolidone in a ratio of 1: 9. The effectiveness of the use of the drug «Korvitin®» in metabolic syndrome has not yet been established, although the antioxidant, anti-inflammatory, metabolite-sensitive properties of quercetin (the active component of the drug «Korvitin®») are well known. Therefore, the purpose of this research was to study the effect of the drug «Korvitin®» on the course of the experimental metabolic syndrome in rats.

The experimental metabolic syndrome in rats was modeled by enriching the diet with fructose (adding fructose to the feed and replacing the drink with a 10.0% fructose solution - in total in the diet up to 20.0% of the daily caloric value) and solid animal fats (lard and fat in total in diet up to 20.0% of daily calories) for 18 weeks.

The results of the study indicate that the use of Korvitin in the therapeutic regimen for 28 days starting from the 15th week of modeling the control pathology was characterized by a positive corrective effect on the level of basal insulin and the HOMA-IR index, respectively, by 1.6 and 1.7 times ($p < 0.05$) is lower than that in the control pathology. A decrease in the severity of manifestations of insulin resistance against the background of the use of Korvitin indicates an improvement in the processes of glucose utilization and the duration of glycemia, which is indicated by a decrease in glycemia during HTSTG (by 1.3-1.5 times; $p < 0.05$), the area under the glycemic curve by 1.3 times ($p < 0.05$) and the HbA1C content by 1.6 times ($p < 0.05$) relative to similar indicators in animals of the experimental metabolic syndrome group.

The effectiveness of the drug «Korvitin®» was established in experimental metabolic syndrome, this is due to the activity of quercetin, a component of the drug, which is characterized by an increase in the sensitivity of cells to the activity of insulin, an improvement in the processes of glucose utilization and the duration of glycemia [19]. The drug was found to be able to improve the state of the vascular endothelium while taking quercetin in rats with experimental metabolic syndrome [20].

Despite the fact that according to all the studied parameters the drug «Korvitin®» was inferior to the highly effective insulin sensitizer metformin, which keep a leading place in the treatment of insulin-resistant conditions [21], it had a rather pronounced therapeutic effect in improving the sensitivity of cells to insulin and affecting glucose homeostasis. Also, the data obtained are the basis for the expansion of the pharmacodynamics of the Korvitin drug with amending the instructions for medical use.

Keywords Korvitin®, quercetin, metabolic syndrome.

Introduction

Korvitin® is an original water-soluble complex of quercetin with polyvinylpyrrolidone in a ratio of 1: 9 [1]. «Korvitin®» has been available on the pharmaceutical market of Ukraine since 2014 and is produced by the Public Joint Stock Company Borshchagovskiy Chemical and Pharmaceutical Factory in Kiev in the form of a lyophilized powder for the preparation of a solution for injection of 0.5 g in vials («Korvitin®» lyophilisate for a solution for injection 0.5 g vial No. 5) [2]. Indications for the use of the drug are complex therapy of acute disorders of coronary circulation and myocardial infarction; treatment and prevention of reperfusion syndrome in the surgical treatment of patients with obliterating atherosclerosis of the abdominal aorta and peripheral arteries [3, 4]. Also in 2020, during the COVID-19 epidemic caused by the SARS-CoV-2 or 2019-nCoV virus, the effectiveness of the drug «Korvitin®» was confirmed as part of the complex treatment of pneumonia caused by Coronavirus infection in adults with appropriate changes to the instructions for medical use of this drug [1].

The modern innovation of off-lable use therapy (prescribing a drug not according to indications in the instructions), which is recognized in almost all countries of the world [6, 7], is based on newly established, previously unknown, pharmacological effects of drugs that were not directly studied during the initial development of the drug, but were discovered after its registration and entry into the pharmaceutical market. An obvious example of the latter is the changes in the indications for the use of the drug «Korvitin®», which are given above.

The effectiveness of the use of the drug «Korvitin®» in metabolic syndrome has not yet been established, although the antioxidant, anti-inflammatory, metabolite-sensitive properties of quercetin (the active component of the drug «Korvitin®») are well known [8, 9, 10].

Therefore, the purpose of this research was to study the effect of the drug «Korvitin®» on the course of the experimental metabolic syndrome in rats.

Methods

Text The analysis of the effectiveness of the drug «Korvitin®» on the course of the experimental metabolic syndrome in rats was carried out by evaluating the effect of the drug on the sensitivity of cells to insulin, glucose utilization and the duration of glycemia.

The experimental metabolic syndrome in rats was modeled by enriching the diet with fructose (adding fructose to the feed and replacing the drink with a 10.0% fructose solution - in total in the diet up to 20.0% of the daily caloric value) and solid animal fats (lard and fat in total in diet up to 20.0% of daily calories) for 18 weeks [11].

Animals were divided into 4 groups of 6 rats: 1 – intact control (IC), animals that were kept on a standard vivarium ration and consumed a diet balanced in the set of proteins, fats, carbohydrates, essential microelements and vitamins; 2 – rats with experimental metabolic syndrome in which the diet has been fortified with fructose and solid animal fats (as indicated above); 3 – rats with experimental metabolic syndrome, which were injected with the drug «Korvitin®» at a dose of 50 mg/kg intraperitoneally (i.p.) («Korvitin®» lyophilisate for the injection region 0.5 g vial No. 5 Borschagovskiy CPF PAO Kiev, Ukraine); 4 – rats with experimental metabolic syndrome, which was injected with metformin at a dose of 60 mg/kg [12] intragastrically (i/g) (tablet "Siofor®" 500 mg produced by Berlin-Chemie AG) [13]. Korvitin® and metformin were administered to the appropriate experimental groups in a therapeutic regimen starting from the 15th week of modeling the experimental metabolic syndrome for 4 weeks (28 days).

The study of the effect of the drug «Korvitin®» and the reference agent metformin on glucose metabolism was carried out by assessing the level of basal glycemia and insulinemia in the blood serum with the subsequent calculation of the HOMA-IR index (homeostatic model assessment of insulin resistance) [14, 14, 15]. The duration of glycemia was assessed by the content of glycosylated hemoglobin (HbA_{1C}) [11]. We also investigated the glycemic response under the influence of the studied drugs by assessing the area under the glycemic curve during the intraperitoneal glucose load test (2 g/kg) [14].

The insulin content in the blood serum was determined by the enzyme immunoassay using a set of reagents DRC_1 Insulin Elisa (Germany). Serum glucose and HbA_{1C} levels were determined spectrophotometrically by use of Filisit-Diagnostics

kits (Ukraine) [14]. Blood glucose was determined by performing an intraperitoneal glucose load test by use of glucometer Contour Plus (Ascensia Diabetes Care). Blood sampling was performed from the tail vein before glucose loading (0 value is the initial level) and at 15, 30, and 45 min after glucose administration by use of unified technique [14].

All these indicators were analyzed by methods of variation statistics (average, its standard error, median, upper and lower quartiles) using parametric (one-way analysis of variance ANOVA, Newman-Keuls test) and nonparametric methods of analysis (Kruskal-Wallis test, Mann-Whitney). Significance level established p<0,05. To obtain statistical conclusions, we used a standard software package «Statistica» [16].

The studies were carried out on the basis of the Educational And Scientific Training Laboratory For Biomedical Research of the Educational and Scientific Institute of Applied Pharmacy of the National University of Pharmacy (NUPh). During the experiment, the animals were kept in the vivarium of the NUPh training center at an air temperature of 20-22 ° C, a natural day-night light regime, in standard cages, on a standard diet. All manipulations with animals were carried out in accordance with the requirements of GLP, recommendations of the State Expert Center of the Ministry of Health of Ukraine, "General Ethical Principles of Experiments on Animals (Ukraine, 2001), Law of Ukraine dated February 21, 2006 No. 3447-IV with amendments" On the protection of animals from cruelty ", the decree and the National Congress on Bioethics (Kiev, 2007) and the European Convention for the Protection of Vertebrate Animals used for experimental or other scientific purposes [17].

Results and discussion

Prolonged stay of rats of the experimental metabolic syndrome group on a diet enriched with fructose and solid animal fats led to the development of insensitivity of animal body cells to the action of insulin, as evidenced by a significant increase in the level of basal glucose by 36.0% (p <0.05) and insulin by 3,0 times; (P <0.05) relative to similar indicators in animals of intact control. This was reflected by changes in the HOMA-IR index - an increase of 4.0 times (p <0.05) relative to intact control rats (table 1).

Violation of the processes of glucose utilization in animals of control pathology under the conditions of the experimental metabolic syndrome was evidenced by a significant increase in glucose levels in all periods: 0, 15, 30, 45 min, respectively in 1.6; 2.9; 2.8; and 2.2 times (p <0.05) and the area under the glycemic curve (2.7 times; p <0.05) during the intraperitoneal glucose tolerance test (IPGTT) (Figure 1, Figure 2).

An increase in the content of glycosylated hemoglobin HbA_{1C} - 2.2 times (p <0.05) relative to animals of intact control indicates an increase in the duration of glycemia in animals of control pathology (Table 1).

The results of the study indicate that the use of Korvitin in the therapeutic regimen for 28 days starting from the 15th week of modeling the control pathology was characterized by a positive corrective effect on the level of basal insulin and the HOMA-IR index, respectively, by 1.6 and 1.7 times (p <0.05) is lower than that in the control pathology. A decrease in the severity of manifestations of insulin resistance against the background of the use of Korvitin indicates an improvement in the processes of glucose utilization and the duration of glycemia, which is indicated by a decrease in glycemia during HTSTG (by 1.3-1.5 times; p <0.05), the area under the glycemic curve by 1.3 times (p <0.05) and the HbA_{1C} content by 1.6 times (p <0.05) relative to similar indicators in animals of the experimental metabolic syndrome group.

The effectiveness of the drug «Korvitin®» was established in experimental metabolic syndrome, this is due to the activity of quercetin, a component of the drug, which is characterized by an increase in the sensitivity of cells to the activity of insulin, an improvement in the processes of glucose utilization and the duration of glycemia [19]. The drug was found to be able to improve the state of the vascular endothelium while taking quercetin in rats with experimental metabolic syndrome [20].

Despite the fact that according to all the studied parameters the drug «Korvitin®» was inferior to the highly effective insulin sensitizer metformin, which keep a leading place in the treatment of insulin-resistant conditions [21], it had a rather pronounced

therapeutic effect in improving the sensitivity of cells to insulin and affecting glucose homeostasis.

Also, the data obtained are the basis for the expansion of the pharmacodynamics of the Korvitin drug with amending the instructions for medical use.

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Table 1. Influence of «Korvitin®» and metformin on indicators of glucose metabolism under the conditions of experimental metabolic syndrome in rats Me (LQ; UQ)

Experimental conditions/investigated indicator	Glucose, mM/l	Insulin, IU/l	HOMA-IR	HbA_{1C}, %
Intact control	4,33 (4,23; 4,51)	0,61 (0,58; 0,65)	0,12 (0,12; 0,12)	1,26 (1,23; 1,29)
Control pathology - experimental metabolic syndrome	5,91* (5,84; 6,03)	1,81* (1,80; 1,84)	0,49* (0,46; 0,49)	2,78* (2,67; 3,00)
Experimental metabolic syndrome treated with Korvitin, 50 mg/kg	5,63@ (5,55; 6,03)	1,15 (1,10; 1,28)	0,29@ (0,27; 0,34)	2,07@ (2,00; 2,12)
Experimental metabolic syndrome treated with metformin, 60 mg/kg	4,42@ (4,30;4,53)	0,75@ (0,70; 0,76)	0,15@ (0,13; 0,16)	1,39@ (1,21; 1,43)

Notes: * – reliably relative to animals of intact control (IC), p<0,05; @ – reliably relative to animals of control pathology (CP), p<0,05.

Figure 1. Glycemic response under the influence of the studied drugs by assessing the area under the glycemic curve during the intraperitoneal glucose load test (2 g/kg)

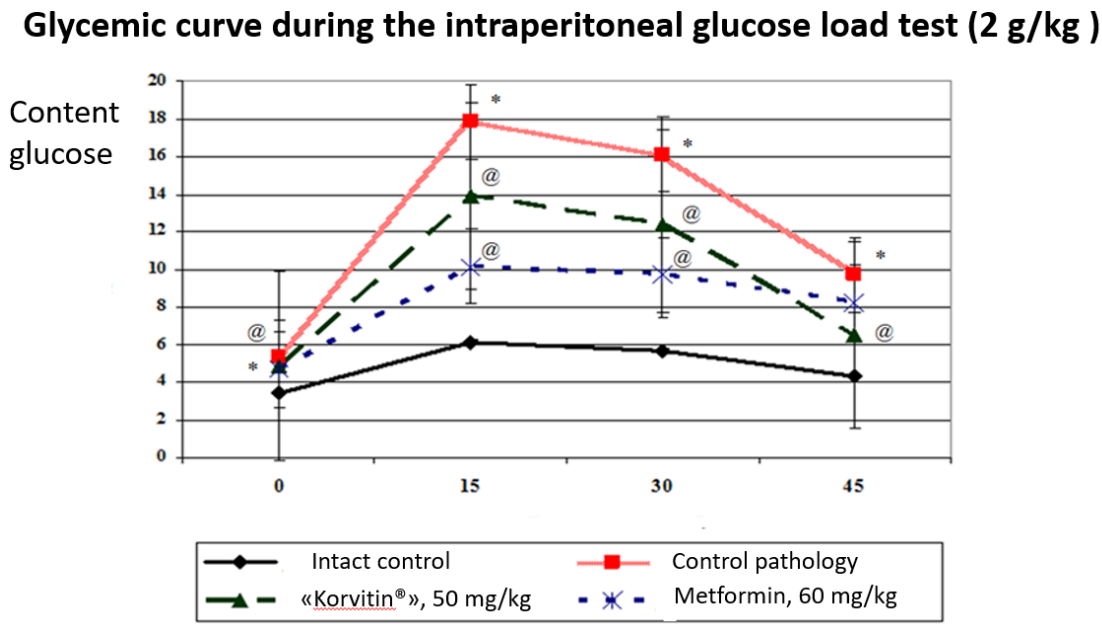

Figure 2. Area under the glycemic curve during the intraperitoneal glucose load test (2 g/kg)