

ADMINISTRATION OF «CORVITIN®» AS AN OFF-LABEL AGENT FOR PHARMACOLOGICAL CORRECTION OF METABOLIC SYNDROME*

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In recent decades occurrence of metabolic syndrome (MS) in the whole world has increased markedly (25–49% of the planet population). This complex of symptoms is really confirmed as a noninfectious pandemic of the XXI century [1]. Till nowadays there is no a unified definition of MS, though the majority of researchers suggest the MS is a body pathology including the following: abdominal obesity, insulin resistance with compensatory hyperinsulinemia; disturbed glucose tolerance; hyperlipidemia; hypertension. It is considered to be a predictor of cardiovascular, endocrine and neurodegenerative diseases [2]. Cardiosclerosis, ischemic heart disease, endothelial dysfunction, arterial hypertension, blood homeostasis disorders resulting in cardiovascular failures: stroke and infarction; cerebrovascular complications; type 2 diabetes mellitus; nonalcoholic liver disease and other endocrine disorders are

separate signs of MS [3]. Individuals with MS are found to have an increased risk of a negative prognosis of sickness and mortality rates due to COVID-19, caused by severe acute respiratory syndrome of coronavirus 2 (SARS-CoV-2), though pathophysiological mechanisms of these interrelations are not determined completely [4].

Today the basic therapy of MS consists of the medicines which pathogenically and symptomatically decrease certain signs of this complex of symptoms: insulin sensitizers, hypolipidemic, anti-hypertensive drugs, antiaggregants, hepatoprotectors etc. [5]. The above assumes polyvector pharmacological correction of MS, which often stipulates administration of several medicines and results in polypragmasy. In order to eliminate the latter, indication of drugs possessing polymorbid, for example, an organ protective action would be reasonable. It

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will enable to produce an additional favorable effect on further prognosis of the pathology.

«Corvitin®» is an original water-soluble form of Quercetin with Polyvinylpyrrolidone in the ratio 1:9. It is produced in the form of a frozen-dried (lyophilized) powder to prepare solution for intravenous injections in the dose of 0,5 g in bottles by Borshchagivsky Chemical-Pharmaceutical Plant, Joint-Stock Company, Kyiv, Ukraine [6]. It is used in a comprehensive therapy of acute disturbance of the cerebral circulation and myocardial infarction; for treatment and prevention of reperfusion syndrome in surgical treatment of patients with obliterating atherosclerosis of the abdominal aorta and peripheral arteries. The drug is well-tolerated by patients.

Off-label administration (that is, administration of a drug not according to the indications in its instruction) is a common practice in medi-

cine: 1 out of 5 indications of drugs in the USA is off-label. Off-label administration of drugs is recognized practically in all the countries of the world [7]. It is based on new determined pharmacological effects of drugs unknown before. These effects were not studied during the primary development of a pharmacological agent, but they were found after its registration and appearance at the pharmaceutical market. In case of certain pathologies off-label administration of medicines becomes especially spread. It is mainly stipulated by the lack of proprietary drugs according to specific indications.

Objective — to study «Corvitin®» effects produced on the parameters of carbohydrate, lipid metabolism and pro-inflammatory status under conditions of experimental metabolic syndrome on golden or Syrian hamsters (*Mesocricetus auratus*).

MATERIALS AND METHOD

Golden hamsters are widely used as a test-system with the aim to study metabolism correcting medicines, since this species of animals is characterized by a maximal similarity of lipoprotein profile to that of the human one [8].

Mature male hamsters aged 6 months and with the body weight of 120–140 g were divided into 4 groups containing 6 animals each:

1. Intact control group (hamsters kept on a standard vivarium forage getting a balanced diet containing proteins, fats, carbohydrates, essential trace elements and vitamins);
2. Control pathology (their forage was 60% changed into fructose in the form of dry feed and drink);
3. Animals of the control pathology, which received Corvitin in the dose of 50 mg/kg (recalculated to Quercetin) [9] injected into the peritoneum («Corvitin®» frozen-dried for injectable solution in 0,5 g bottles № 5 produced by Borshchagivsky Chemical-Pharmaceutical Plant, Joint-Stock Company, Kyiv, Ukraine),
4. Animals of control pathology, which received Metformin in the dose of 60 mg/kg administered into the stomach (tablets «SIOFOR®» 500 mg produced by Ltd Berlin-Chemie) [10].

The control pathology was simulated by means of Changiz Taghibiglou et al. method [11]. During 14 days the following groups of animals: 2 (control pathology), 3 (control pathology+Corvitin) and 4 (control pathology+Metformin) were kept on the diet 60% changed into fructose in the form of dry feed and drink (further — 60% fructose diet). Beginning with the 15th day of the experiment with underlying 60% fructose diet the groups 3 and 4 began to receive Corvitin under study and reference Metformin during 10 days. During this whole time the animals from group 2 (control pathology) were kept on 60% fructose diet, and the animals from group 1 (intact control) were kept of the standard vivarium forage getting a balanced diet containing proteins, fats, carbohydrates, essential trace elements and vitamins.

The effects of Corvitin and Metformin produced on the parameters of carbohydrate metabolism were studied by the assessment of glucose and insulin concentration in the blood serum, and calculation of HOMA-IR. The following parameters of lipid type were examined: the level of the whole lipids, cholesterol, apolipoprotein B (apoB) and triglycerides (TG). The following cytokines were considered as markers of pro-inflammatory status: IL-1 β , IL-6, TNF- α [12].

The concentration of insulin and cytokines was determined by means of immune-enzyme assay with the set of reagents DRC1 Insulin Elisa (Germany) and «Vector-Best» Firm (Russian Federation) respectively. The concentration of apolipoprotein B was determined by means of immune-turbodimetric method using reagents produced by DIALAB (Austria). The levels of glucose, whole lipids, cholesterol and TG were determined by means of spectrophotometric methods with the use of sets «Felic-Diagnostics» (Ukraine).

RESULTS AND THEIR DISCUSSION

The hamsters from the control pathology group kept on 60% fructose diet developed increase of the basal glucose level (2,2 times as much, $p < 0,05$), insulin (5,6 times, $p < 0,05$) and integral index HOMA-IR more than 12 times as much ($p < 0,05$), which is indicative of severity of the simulated pathology (Table 1).

The results of the study are indicative of the fact that Corvitin given to hamsters with underlying severe metabolic syndrome is able to improve cellular sensitivity to insulin: HOMA-IR decreased by 35%, ($p < 0,05$); the levels of basal glycemia and insulinemia decreased, and the concentration of glucose and insulin decreased 1,4 and 1,2 times respectively ($p < 0,05$) concerning similar parameters in the animals from the group of control pathology.

Under conditions of hyperinsulinemia and reduced sensitivity to insulin in the adipose tissue, especially in the visceral one, lipolysis is intensified and transportation of free fatty acids into the liver increase, that in general results in development and advance of dyslipidemia [13, 14]. Thus, in the group of hamsters with control pathology the concentration of whole lipids increased by 63,5% ($p < 0,05$), cholesterol by 38,5% ($p < 0,05$), apoB by 67,2% ($p < 0,05$) and TG 2,6 times ($p < 0,05$) (Table 2).

Analysis of Table 2 indicates that Corvitin administration corrected pathological dyslipidemia, which is confirmed by a decreased level of whole lipids, cholesterol, lipoproteid, apoB and TG by 8, 41, 27 and 17% respectively ($p < 0,05$).

The effect of signal molecules (cytokines) produced by the adipose tissue cells on the body

The results obtained were statistically processed by means of the computer program Statistica 6,0 (StatSoft, Inc., USA), normal distribution was checked by means of *Shapiro-Wilk's* method for normality. The data obtained were found to be subject to abnormal distribution, therefore, non-parametric Mann-Whitney U test was used. The results were presented as median (Me) and interquartile range (25–75 percentiles). Confidence interval was $p < 0,05$ [13].

results in advance of disorders intensifying pathological process [15]. Thus, under conditions of control pathology the levels of proinflammatory cytokines increased: IL-1 β — 2,35 times and IL-6 and TNF- α — 3,2 times ($p < 0,05$), which is indicative of development and advance of subchronic inflammatory process (Table 3). In its turn, TNF- α disturbs insulin signals in the adipose tissue and skeletal muscles, promotes formation of insulin resistance and compensatory hyperinsulinemia, which can be considered as an early prognostic marker of type 2 diabetes mellitus. An increased level of IL-6 is in direct proportion to reduced sensitivity of tissues to insulin, while increased concentration of IL-1 β is a signal of development of subchronic inflammatory process in the body [16].

Results of the study are indicative of the fact that Corvitin administration reduced considerably the signs of systemic inflammation which is confirmed by reduced levels of IL-1 β , IL-6, TNF- β by 41, 62 and 48,5% respectively ($p < 0,05$). At the same time, concerning the effect produced on the course of proinflammatory status, Corvitin effect was reliably more significant than that of the reference Metformin, which decreased the content of proinflammatory cytokines IL-1 β , IL-6, TNF- β by 30, 37 and 14% respectively ($p < 0,05$).

Therefore, the results of the study conducted enabled to establish a favorable Corvitin effect produced on the course of metabolic syndrome found under conditions of experimental simulation of the pathology in hamsters. All the above substantiates reasonability to indicate off-label administration of the drug in therapy of metabolic syndrome with the aim

to increase efficacy and safety of its treatment. Moreover, the results obtained are the basis for wider pharmacodynamics of the drug

«Corvitin®» and introduction of certain changes into the instruction of its medical administration.

Table 1

Corvitin effect on the parameters of insulin resistance and glycemia duration Me (LQ; UQ)

Terms of the experiment / parameter under study	Glucose, mM/L	Insulin, mcMU/ml	HOMA-IR
IC	4,00 (3,85; 4,11)	2,20 (2,09; 2,28)	0,39 (0,37; 0,41)
CP	8,78* (8,11; 9,01)	12,44* (12,27; 13,00)	4,77* (4,66; 4,91)
Corvitin, 50 mg/kg	6,47*/@ (6,42; 6,54)	10,66*/@ (10,45; 11,25)	3,12*/@ (3,00; 3,31)
Metformin, 60 mg/kg	3,51@ (3,28; 6,44)	2,34@ (2,27; 2,79)	0,41@ (0,35; 0,67)

Notes:

- * reliable concerning the animals of intact control (IC), p < 0,05;
- @ reliable concerning the animals of control pathology(CP), p < 0,05.

Table 2

Corvitin effect produced on the lipid type parameters Me (LQ; UQ)

Terms of the experiment / parameter under study	Whole lipids, g/L	Cholesterol, mM/L	apoB, mc/gL	TG, mmol/L
IC	4,08 (3,81; 4,22)	4,97 (4,69; 5,13)	65,90 (65,34; 66,48)	0,61 (0,55; 0,65)
CP	6,67* (6,44; 7,03)	6,89* (6,58; 7,08)	110,17* (108,85; 122,05)	1,56* (1,44; 1,72)
Corvitin, 50 mg/kg	6,12*/@ (6,03; 6,23)	4,06*/@ (3,92; 4,12)	80,65*/@ (79,66; 81,66)	1,29*/@ (1,24; 1,33)
Metformin, 60 mg/kg	4,64*/@ (4,36; 4,82)	7,00*/@ (6,69; 7,12)	90,47*/@/€ (88,65; 92,13)	1,09*/@ (0,92; 1,12)

Notes:

- * reliable concerning the animals of intact control (IC), p < 0,05;
- @ reliable concerning the animals of control pathology(CP), p < 0,05;
- € reliable concerning the animals of Corvitin group, p < 0,05.

Table 3

Corvitin effect produced on the parameters of pro-inflammatory status Me (LQ; UQ)

Terms of the experiment / parameter under study	IL-1 β, pcg/ml	IL-6, pcg/ml	TNF-α, pcg/ml
IC	25,22 (24,62; 26,00)	8,66 (8,22; 9,22)	12,73 (12,08; 13,00)
CP	59,28* (58,42; 60,00)	28,12* (26,86; 29,08)	40,94* (39,53; 46,42)
Corvitin, 50 mg/kg	30,45*/@ (29,77; 31,85)	10,75*/@ (10,49; 11,00)	21,08*/@ (21,00; 21,65)
Metformin, 60 mg/kg	41,22*/@/€ (40,38; 42,00)	17,77*/@/€ (17,15; 18,34)	35,08*/@/€ (34,25; 36,12)

Notes:

- * reliable concerning the animals of intact control (IC), p < 0,05;
- @ reliable concerning the animals of control pathology(CP), p < 0,05;
- € reliable concerning the animals of Corvitin group, p < 0,05.

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Nowadays metabolic syndrome is a noninfectious pandemic of the XXI century. Therefore search of effective pharmacological agents for its pharmacological correction is an urgent issue of modern medicine and pharmaceutical community. At the same time, today off-label administration of medicines (for an unapproved indication) has become widely used. This approach is based on new determined pharmacological effects of drugs unknown before. These effects were not studied during the primary development of a pharmacological agent, but they were found after its registration and appearance at the pharmaceutical market.

The article presents the results of the experimental study of metabolism correcting properties of the drug «Corvitin®» (a frozen-dried (lyophilized) powder to prepare solution for intravenous injections in the dose of 0,5 g in bottles by Borshchagivsky Chemical-Pharmaceutical Plant, Joint-Stock Company, Kyiv, Ukraine under conditions of experimental metabolic syndrome on golden or Syrian hamsters (*Mesocricetus auratus*).

The control pathology was simulated by means of Changiz Taghibiglou et al. method. During 14 days the following groups of animals: 2 (control pathology), 3 (control pathology + Corvitin) and 4 (control pathology + Metformin) were kept on the diet 60 % changed into fructose in the form of dry feed and drink (further — 60 % fructose diet). Beginning with the 15th day of the experiment with underlying 60 % fructose diet the groups 3 and 4 began to receive Corvitin under study and reference Metformin during 10 days. During this whole time the animals from group 2 (control pathology) were kept on 60% fructose diet, and the animals from group 1 (intact control) were kept of the standard vivarium forage getting a balanced diet containing proteins, fats, carbohydrates, essential trace elements and vitamins.

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above substantiates reasonability to indicate off-label administration of the drug in therapy of metabolic syndrome with the aim to increase efficacy and safety of its treatment. Moreover, the results obtained are the basis for wider pharmacodynamics of the drug «Corvitin®» and introduction of certain changes into the instruction of its medical administration.

Key words: Corvitin, metabolic syndrome, off-label.

ЗАСТОСУВАННЯ ПРЕПАРАТУ «КОРВІТИН®» ЯК ЗАСОБУ «OFF-LABLE» ДЛЯ ФАРМАКОКОРЕКЦІЇ МЕТАБОЛІЧНОГО СИНДРОМУ

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Метаболічний синдром на сьогодні є неінфекційною пандемією ХХІ століття. Тому пошук ефективних лікарських засобів для його фармакокорекції є актуальним питанням сучасної медичної та фармацевтичної спільноти. Разом з тим широке застосування на сьогодні набуває призначення лікарських засобів *off-label* (не за показаннями в інструкції) у випадку виявлення раніше невідомих фармакологічних ефектів препарату щодо до таких, які зазначені в інструкції до медичного застосування.

В даній статті представлені результати експериментального вивчення метаболітокорегувальних властивостей препарату «Корвітин®» (ліофілізат р-ну для ін'єкцій 0,5 г фл. № 5, Борщагівський ХФЗ ПАТ Київ, Україна) за умов експериментального метаболічного синдрому у сирійських золотавих хом'яків.

Контрольну патологію відтворювали методом Changiz Taghibiglou et al., а саме протягом 14 днів групи тварин: 2 (контрольна патологія), 3 (контрольна патологія + корвітин) та 4 (контрольна патологія + метформін) перебували на харчовому раціоні який на 60 % був замінений на фруктозу у вигляді сухого корму та пиття (в подальшому — раціон 60 % фруктоза). Починаючи з 15 дня експерименту на тлі продовження перебування на раціоні 60% фруктоза група 3 та 4 почали отримувати досліджуваний (корвітин) та референтний (метформін) препарати протягом 10 днів. Весь цей час група 2 (контрольна патологія) перебували на раціоні 60 % фруктоза, а група тварин 1 (інтактний контроль) утримувалися на стандартному раціоні віварію та споживали збалансований за набором білків, жирів, вуглеводів, необхідних мікроелементів та вітамінів харчовий раціон. Вивчення впливу корвітину та метформіну на показники вуглеводного обміну проводили за оцінкою вмісту глюкози та інсуліну в сироватці крові, розрахунку індексу НОМА-ІР. Як показники ліпідного профілю досліджували рівень загальних ліпідів, холестеролу, аполіпопротеїну В (apoB) та тригліцеридів (ТГ). Маркерами прозапального статусу слугували такі цитокіни: ІЛ-1 β, ІЛ-6, ФНП-α.

Результати проведених досліджень дозволили встановити сприятливий вплив корвітину на перебіг метаболічного синдрому, яка виявлена за умов експериментального метаболічного синдрому у хом'яків. Це обґрунтовує доцільність застосування даного препарату в *off-label* терапії метаболічного синдрому з метою підвищення ефективності та безпечності його лікування. Також отриманні дані є підґрунтями для розширення фармакодинаміки препарату корвітин з внесенням змін до інструкції з медичного застосування.

Ключові слова: корвітин, метаболічний синдром, off-label.