O. M. RADCHENKO, L. M. STRILCHUK, Z. M. KIT, I. B. ZHAKUN, O. O. SOROKOPUD, M. O. KONDRATYUK (Lviv, Ukraine)

USAGE OF URSODEOXYCHOLIC ACID IN CARDIOLOGY
(literature review and own data)

Danylo Halytsky Lviv National Medical University <larysa.stril4uk@ukr.net>

Ursodeoxycholic acid (UDCA) influences bile formation and excretion. Apart from that, UDCA has some pleiotropic effects, which can be a basis for usage of this drug for treatment of cardiovascular diseases. We held a scientific literature review in PubMed database and domestic literature sources according to key words “ursodeoxycholic acid”, “chenodeoxycholic acid”, “enterohepatic circulation”, “bile acids”. It was revealed that UDCA has a wide spectrum of action because of its cytoprotective, anti-apoptotic, anti-inflammatory, antioxidative and immune-modulating effects, which are of particular importance in cardiology. Some authors propose to use UDCA in patients with ischemic heart disease, especially in case of comorbid metabolic syndrome and nonalcoholic steatohepatitis. We determined the level of leptin in the blood by immunoenzyme method in 43 patients with arterial hypertension before and after a month of outpatient treatment by atorvastatin or UDCA. It was shown that both drugs led to significant decrease of blood serum atherogenic influence due to decrease of total cholesterol and cholesterol of low-density lipoproteins (more expressed in the statin group) and due to decrease of previously increased leptin level (more expressed in the UDCA group). Investigation of drug influence on adipocytokines synthesis in patients with cardiovascular diseases is perspective in terms of its correction possibilities.

Key words: ursodeoxycholic acid; leptin; atorvastatin; cardioprotection.

Introduction. Modern science changed standard views onto bile acids (BA) role in organism. They are now considered to be the signal molecules of systemic regulation, which influence numerous metabolic reactions [8]. Ursodeoxycholic acid (UDCA), which is one of the BA, influences bile formation and excretion. Apart from that, UDCA has some pleiotropic effects, which can be a basis for usage of this drug in treatment of patients with cardiovascular diseases. Investigation and usage of UDCA pleiotropic effects is especially important for treatment of people with multiple comorbid conditions and elderly patients, because it could prevent polypragmasia and allow pharmacotherapy optimization. However, usage of UDCA in cardiology is not sufficiently studied yet, that’s why this topic was chosen for our paper.

The aim of this article is to describe modern scientific views onto mechanisms of UDCA pleiotropic effects and its usage in cardiology (literature review). Apart from that, we aimed to estimate UDCA influence onto lipid parameters and leptin level in patients with arterial hypertension.

Materials and methods. We held a scientific literature review in PubMed database and domestic literature sources according to key words “ursodeoxycholic acid”, “chenodeoxycholic acid”, “enterohepatic circulation”, “bile acids” (about 5000 links). We also estimated leptin level by immunoenzyme method (“DRG Leptin ELISA”, Germany) and lipid parameters by standard methods in 43 patients with arterial hypertension of 2nd stage and 2nd grade, who were treated by lysinopril (10–20 mg daily) as a basic treatment together with atorvastatin (10 mg daily for 4 weeks) (n = 23; 4 men and 19 women, mean age 65.5 years ± 1.5 years, body mass index (BMI) 33.80 kg/m² ± 1.08 kg/m², waist circumference 100 cm ± 2 cm, hip circumference 115.5 cm ± 2.4 cm)
or UDCA (Ursochol, "Darnytsya", Ukraine, 10 mg/kg of bodyweight) (n = 20; 5 men and 15 women, mean age 63.4 years ± 1.9 years, waist circumference 99.3 cm ± 1.4 cm, hip circumference 108.8 cm ± 2.3 cm, BMI 33.1 kg/m² ± 1.0 kg/m², both P > 0.05). Data was processed by statistic methods using Student’s criterion; estimation of treatment was held by Wilkoxon criterion (Wst) (Wilcoxon signed-ranks test for matched pairs).

**Results and discussion.** According to the literature data, UDCA is an epimer of primary chenodeoxycholic BA (tertiary BA), which differs by the change of hydroxyl group position. Despite that UDCA only accounts for about 5 % of all BA, it has a significant influence on the whole organism. This was known since ancient times, when bear bile was found to be a curing agent, which still is used in Chinese traditional medicine. According to modern data, BA are the signal molecules with systemic influence. First of all, they activate a range of bioactive agents – MAP-kinase, TGR5, farnesoid X receptor α (FXRα) and also induce the expression of cholesterol-7α hydrolase (CYP7A1) and receptors to cholesterol of low density lipoproteins (LDL-C) in liver [13, 17, 18]. Via FXRα, which regulates gene transcription, BA influence not only their own homeostasis, but also regulate lipid and carbohydrate metabolism [8].

Despite the main effects of ursodeoxycholic acid (UDCA) are known [2, 8, 16], its mechanisms of action are still being studied. Anticholestatic, choleretic and litholytic effects of UDCA stipulate the main usage of this drug, namely, therapy of cholestasis, cholelithiasis, hepatitis, liver cirrhosis. But it was revealed that UDCA has a much wider spectrum of action because of its cytoprotective, anti-apoptotic, anti-inflammatory, antioxidative and immune-modulating effects, which are of especial value in cardiology [8, 18, 19].

**Cytoprotective** effect is a result of direct installation of UDCA molecule into the phospholipid layer of cellular membrane. This leads to membrane stabilization and increases cell resistance to various damages [13], which is especially important for protection against xenobiotics’ action. UDCA also increases cardiomyocytes’ resistance to hypoxia [19]. **Anti-apoptotic** effect of UDCA is provided mainly by decrease of Ca²⁺ concentration in the cells, prevention of cytochrome C exit from the mitochondria, decrease of caspases’ activation [12, 13]. **Hypocholesterolic** effect and lipid metabolism normalization by UDCA are based on decrease of cholesterol absorption in guts, inhibition of its synthesis in liver, activation of cholesterol excretion to the bile and increase of excretion of cholesterol of very low density lipoproteins (VLDL-C) [14, 17]. UDCA stimulates FXRα and activates some mechanisms of lipid utilization: increase of amount of nuclear peroxisome proliferator-activated receptors (PPAR), increase of amount of tissue receptors to LDL-C, activation of lipoproteinlipase in plasma. Apart from that, cholesterol-7α hydrolase (CYP7A1) enzyme, which is also activated by UDCA, controls cholesterol level in liver [17]. It is also important that UDCA is able to form so-called liquid crystals together with cholesterol molecules, which prevents the last from absorption in gut. Hypocholesterolic effect of UDCA was described for the first time only about 15 years ago by the group of scientists under the guidance of R. Poupon. In their investigations UDCA was administered for 2 years as a treatment of primary biliary liver cirrhosis. Later their results were proved by other authors [11]. **Anti-inflammatory** action of UDCA is a result of the decrease of bioactive agents’ production, firstly, transforming growth factor α and pro-inflammatory tumor necrosis factor α, which increases insulin resistance [22]. **Antioxidative** effect of UDCA is a result of previously described membrane stabilization and limitation of oxidative stress via increase of the glutathione level [12, 15, 16, 22]. One more mechanism of antioxidative action takes its roots in increase of cellular resistance to hypoxia via activation of specific enzymes sphingomyelinases [19]. Immunomodulating effect of UDCA manifests through decrease
of expression of histocompatibility molecules HLA, steroid-like properties via transcription of glucocorticoid receptors, decrease of abnormal production of immunoglobulin and cytokines by macrophages, inhibition of immune interactions between T-lymphocytes and epitheliocytes [6], restoration of natural killer cells’ action [21].

Clinical results of UDCA usage were investigated in many works (about 3500 [5]), but scientific debates still continue. Standard indications for UDCA usage include various kinds of hepatitis, liver cirrhosis, atresia of intrahepatic biliary ducts, all kinds of cholestasis; cystic fibrosis of liver; biliary ducts’ dyskinesia; biliary reflux-gastritis and reflux-esophagitis; gallstones of cholesterol origin [2, 9], including cholelithiasis in pregnant women [20]. Although it is not included into official guidelines, different authors propose to use UDCA in patients with ischemic heart disease (IHD), especially in case of comorbid metabolic syndrome and nonalcoholic steatohepatitis [1, 3, 4, 7, 10, 16].

According to the results of investigation, held in our university, additional administration of UDCA to patients with IHD and nonalcoholic fatty liver disease during one-year follow-up period led to the significant decrease of transaminases and cholestasis markers (alaninaminotransferase: from 45.28 units ± 13.89 units to 23.54 units ± 11.32 units, P < 0.001; aspartataminotransferase: from 43.91 units ± 12.65 units to 23.54 units ± 11.32 units, P < 0.001; γ-glutamyl transferase: from 66.65 units ± 9.79 units to 48.34 units ± 8.11 units, P < 0.001; alkaline phosphatase: from 77.14 units ± 8.67 units to 35.56 units ± 5.64 units, P < 0.001) [1]. Apart from that, there was noticed the regress of left ventricle hypertrophy and remodeling, increase of the speed of mitral annulus systolic motion, decrease of ischemia symptoms and frequency of ventricular rhythm disorders [3].

There is an interesting finding that administration of UDCA to pregnant women decreases the amount of cardiomyofibroblasts and prevents cells’ depolarization, induced by hypoxia. This finding can become a base for a perspective investigation of UDCA as an antifibrotic and antiarrhythmic drug for prophylaxis of fetus arrhythmias and heart failure [23].

Due to UDCA cardioprotective effects, we aimed to estimate its influence onto lipid parameters and leptin level in patients with arterial hypertension.

**According to own data**, UDCA has prominent hypocholesterolic and hypoleptinemic action. It is worth to notice that described side effects of UDCA (diarrhea, increase of transaminases level, allergic reactions, skin itching, nausea, pain in right hypochondrium) were not revealed in investigated patients. All participants stated good tolerance and the improvement of subjective well-being.

Influence of UDCA on lipid metabolism parameters was alike to statins – there was noticed significant decrease of blood serum atherogenicity. First of all, it was proved by significant decrease of general cholesterol level (UDCA: from 5.3 mmol/l ± 0.2 mmol/l to 4.9 mmol/l ± 0.2 mmol/l, P < 0.01 according to Wst, statin: from 6.1 mmol/l ± 0.2 mmol/l to 5.4 mmol/l ± 0.2 mmol/l, P < 0.001) and LDL-C (UDCA: from 3.3 mmol/l ± 0.2 mmol/l to 3.0 mmol/l ± 0.2 mmol/l, P < 0.05 according to Wst; statin: from 3.7 mmol/l ± 0.2 mmol/l to 3.2 mmol/l ± 0.2 mmol/l, P < 0.05) on the background of moderate increase of high density lipoproteins (P > 0.05 for both drugs). At the same time, it was shown that UDCA usage less prominently decreased triglycerides (P > 0.05) level then atorvastatin (from 2.4 mmol/l ± 0.4 mmol/l to 2.0 mmol/l ± 0.2 mmol/l, P < 0.05 according to Wst). So, UDCA and atorvastatin decreased general cholesterol level by 7.4 % and 11.1 % (both P < 0.05), LDL-C – by 10.3 % and 15.7 % (both P < 0.05), triglycerides – by 8.6 % (P > 0.05) and 15.6 % (P < 0.05) accordingly. Taking these values into account, we can say that hypocholesterolic effect of UDCA was comparable to atorvastatin action.

Correction of the excessive production of leptin is an important problem of treatment of patients with arterial hypertension and overweight/obesity, because increased
leptin level is associated with increased risk of myocardial infarction and stroke independent of any other cardiovascular risk factors. Our estimation of leptin dynamics for a month therapy by UDCA or atorvastatin showed that leptin level in UDCA group decreased by 26.5% – from 225.5 ng/ml ± 32.3 ng/ml to 165.6 ng/ml ± 27.3 ng/ml (P < 0.05 according to Wst) and in atorvastatin – only by 6.6% from 240.2 ng/ml ± 27.3 ng/ml to 224.3 ng/ml ± 27.5 ng/ml (P > 0.05).

Normalizing action of atorvastatin and UDCA onto leptin production was not described before. According to our point of view, this action is realized through decrease of bioactive substances’ production. UDCA stabilizes membranes and limits oxidative stress via increase of glutathione level and detergent influence onto lipid components, mitochondria membranes and endoplasmatic reticulum. Chronic hyperleptinemia contributes to arterial pressure increase via damage of the depressor mechanisms and hyperproduction of endothelin-1, which is a potent vasoconstrictor agent and a trigger of vessels’ remodeling. Taking these facts into account, hypoleptinemic properties of UDCA, revealed by us, are an important aspect of clinical usage of this drug in complex therapy of cardiological patients with overweight or obesity.

Conclusions. Cytoprotective, antiapoptotic, hypocholesterolic, anti-inflammatory, antioxidative and immunodulating actions of UDCA can be a background of its usage in cardiology, especially in case of comorbidity with non-alcoholic fatty liver disease and overweight or obesity. Inclusion of UDCA into the standard therapy scheme of arterial hypertension leads to significant decrease of blood atherogenicity and previously increased leptin level. That’s why patients with overweight or obesity should start metabolic disorders correction from UDCA. Studying of pleiotropic effects of UDCA needs more investigations; so also does its influence onto adipocytokine circulation in people with cardiovascular disorders.

All authors state absence of conflict of interest. Authors did not receive any payment for their investigation and did not collaborate with any drug manufacturers.

References


4. Кіт З. М., Стрілчук Л. М. Вплив аторвастатину та урсодезоксихолевої кислоти на вміст лептину в крові у хворих на артеріальну гіпертензію // Буков. мед. вісн. – 2015. – 1. – С. 73–75.

Урсодезоксихолевая кислота (УДХК) влияет на образование и выделение жёлчи. Кроме того, УДХК обладает рядом плейотропных эффектов, которые могут быть основой для её использования в лечении больных кардиоваскулярного профиля. Нами проведён поиск в базе данных PubMed и отечественных литературных источниках по ключевым словам "урсодезоксихолевая кислота", "хенодезоксихолевая кислота", "энтерогепатическая циркуляция", "жёлчные кислоты". Было обнаружено, что УДХК обладает широким спектром свойств, в том числе цитопротективных, антиапоптотических, противовоспалительных, антиоксидантных и иммуномодулирующих, имеющих важное значение в кардиологии. Некоторые авторы предлагают назначать УДХК больным ишемической болезнью сердца, особенно в случае коморбидного метаболического синдрома или неалкогольного стеатогепатита. Определение уровня лептина в крови иммуноферментным методом у 43 больных с артериальной гипертензией в динамике до и через 1 мес амбулаторного лечения с использованием аторвастатина или УДХК показало, что оба препарата обусловили сущестовенное снижение атерогенности сыворотки крови за счёт уменьшения уровня общего холестерина и холестерина липопротеинов низкой плотности, более выраженные у статина, и снижение повышенного уровня лептина, более выраженного у жёлчной кислоты. Изучение влияния лекарственных средств на синтез адипоцитокинов у пациентов с сердечно-сосудистыми заболеваниями является перспективным с точки зрения возможностей коррекции.

Ключевые слова: урсодезоксихолевая кислота; лептин; аторвастатин; кардиопротекция.