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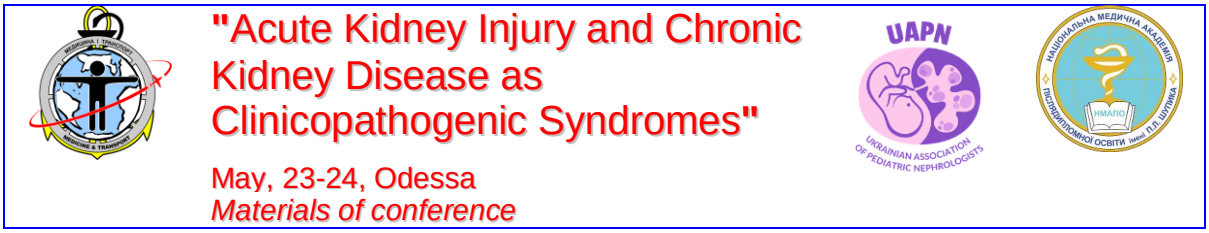

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Morphological changes in kidney glomeruli of rats with chronic toxic hepatitis and its correction with lisinopril, L-arginine-L-glutamate and their combination

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Abstract

The article presents structural changes of glomerular component of kidneys in rats with chronic toxic hepatitis (CTH) and the results of its correction with lisinopril and L-arginine L-glutamate. The influence of ACE inhibitors or angiotensin-blockers (AT) II on RAS chains is known to result in positive therapeutic effect. Addition of lisinopril to complex therapy has positively affected not only the clinical manifestations of the disease but also the functional status of kidneys, primarily due to the influence on filtration processes.

Considering the significance of RAS activation in the development of hepatorenal syndrome, the aim of the work was to study the influence of ACE inhibitors (lisinopril) on

kidney morphological structure during modeling of CTH, to compare its effect with hepatoprotector L-Glutargin-L-glutamate as well as to evaluate structural changes in kidney glomeruli after combined use of those drugs. The experimental study was conducted on 60 white laboratory immature rats, with initial body weight of 50-70g. CTH was modeled by intragastric administration of CCl4 oil solution in a dose of 0.1 ml / 100 g of the body weight twice a week for eight weeks. Drug correction was performed by introduction of lisinopril (in a dose of 20 mg / kg) and L-arginine-L-glutamate (in a dose of 30 mg / kg).

The study revealed pronounced morphological changes in kidney glomeruli (destruction of glomerular vessels and cells) in CTH. The use of corrective factors in the experiment made it possible to decrease the severity of pathological changes. The use of lisinopril resulted in restoration of glomerular structure. After administration of L-arginine-L-glutamate, decrease of degenerative changes in kidney glomeruli was detected. Combined use of both chemical compounds mutually potentiated their action and was accompanied by membrane-stabilizing effect and intensification of aforementioned restoration processes in structural components of nephron glomeruli. Thus, it was established that after 90 days of experimentally modeled CTH, pronounced morphological changes in kidney glomeruli (destruction of vessels and glomerular cells) occurred.

Key words: chronic toxic hepatitis, rats, lisinopril, L-arginine-L-glutamate, morphological changes in kidney glomeruli

Introduction. Hepatorenal syndrome (HRS) is characterized by the development of renal failure in patients with severe liver diseases in the absence of other causes of kidney disorders. According to literature data, HRS occurs in 10% of patients admitted for liver cirrhosis and ascites. 18% of patients develop clinical symptoms of hepatic decompensation during the first year of disease, and 39% - in 5 years [4]. HRS is considered to be a variant of functional renal failure in acute or chronic liver disease [5].

Tetrachloromethane, which exerts hepatotoxic action, causes renal dysfunction by HRS mechanism involving renin-angiotensin system (RAS), and by detrimental effect on renal parenchyma [9]. There are two types of RAS – systemic (circulating) and local (tissue). The mechanisms of systemic and local RAS are not fully understood, but it is the blockage of tissue RAS that nephroprotective effect of angiotensin-converting enzyme (ACE) inhibitor is based upon in various diseases [3, 8].

The influence of ACE inhibitors or angiotensin-blockers (AT) II on RAS chains is known to result in positive therapeutic effect [1, 2]. Addition of lisinopril to complex therapy

has positively affected not only clinical manifestations of the disease but also the functional status of kidneys, primarily due to the influence on filtration processes [3, 4].

Considering the essential role of RAS activation in HRS development [7], the aim of the study was to investigate the influence of ACE inhibitor on morphological changes in kidneys by modeling chronic toxic hepatitis (CTH) [12], as well as to compare its action with that of L-arginine-L-glutamate, and to evaluate structural changes in kidney glomeruli after combined use of those drugs.

Objective: To study morphological changes in kidney glomeruli of rats with chronic toxic hepatitis and its correction with lisinopril, L-arginine-L-glutamate and their combination.

Materials and methods. An experimental study was performed on 60 non-linear white immature laboratory rats weighting 60-80 grams. The experiments were done in accordance with general principals of animal experiments adopted by I National Bioethical Congress (Kiev, 2001), European Convention for the protection of vertebrate animals used for experimental and other scientific purposes (Strasbourg, 1986), European Community's Council Directive No 609 (1986), and the Order of Ministry of Health of Ukraine No 218 of November 1, 2000 "On measures to improve organizational norms in work with experimental animals". The animals were divided into five experimental groups (12 rats in each group). Group 1 consisted of intact rats. Chronic toxic hepatitis was modeled in the animals of groups 2, 3, 4 and 5 by intragastric administration of CCl_4 Solutio oleosa in the dose of 0.1 ml/100 g of body weight and 5% ethanol solution twice a week for eight weeks [6]. The rats of group 2 received no other agents. Along with hepatotoxins, animals of the remaining groups received ACE inhibitor lisinopril (“Lisinopril”, LLC “Astrapharm”, Ukraine) in therapeutic and prophylactic dose of 20 mg/kg/day [11] for six weeks (group 3), intragastric L-glutargine-L-glutamate 0.75g, (“Glutargin”, LLC "Zdorovya", Ukraine) in therapeutic and prophylactic dose of 30 mg/kg/day [11] for six weeks (group 4**)**, intragastric 20% CCl_4 Solutio oleosa in the dose of 0.1 ml/100 g of body weight twice a week in combination with 5% ethanol solution, as well as L-glutargine-L-glutamate 0.75g, (“Glutargin”, LLC "Zdorovya", Ukraine) in the dose of 30 mg/kg and lisinopril in the dose of 20 mg/kg (“Lisinopril”, LLC “Astrapharm”, Ukraine) (group 5). For histological examination renal tissue samples were embedded in celloidin-paraffin after their fixation in 10% neutral formaline solution and preparation in ethanol solutions of increasing concentrations. Paraffin 4-6 mcm sections were prepared on sliding microtome. Specimen staining was performed with haematoxylin and

eosin. Histologic samples were examined under optical digital microscope Bresser (Germany), magnification - 100-800 x.

Results and discussion. Investigation of renal tissue structure in rats with CTH has revealed the following morphological changes: increased glomeruli size, sharply enlarged capsular spaces due to effusion, shrunken glomeruli of renal corpuscles, uneven (mostly decreased) blood filling of glomerular vessels, damaged basement membranes (Fig. 1).

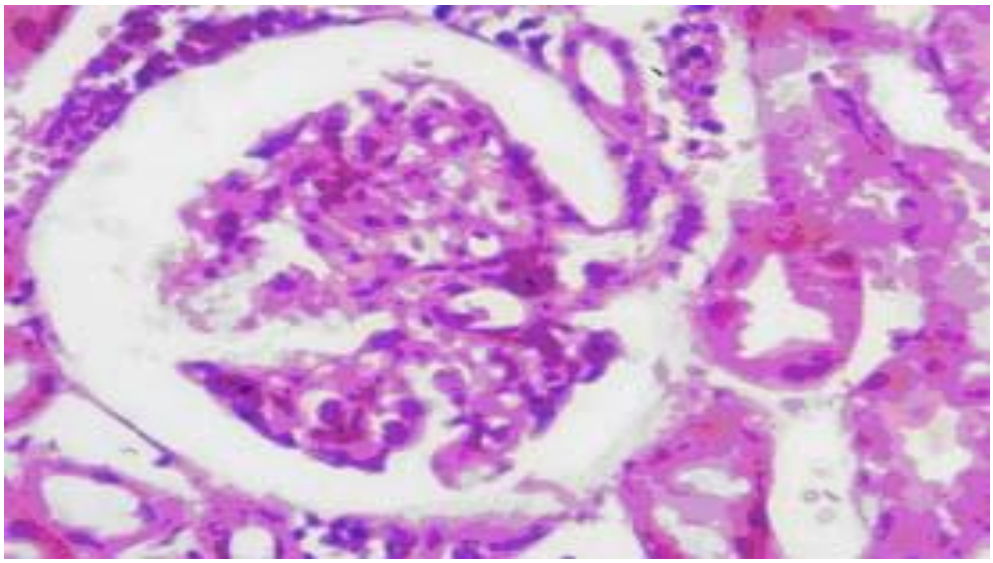

Fig.1. Structure of kidney glomerular component in toxic hepatitis in 90 days. Vascular and cellular glomerular destruction, focal tubular necroses. Staining with haematoxylin and eosin × 200.

After L-arginine-L-glutamate correction less pronounced structural changes were revealed. Uneven blood filling of glomerular vessels was still noted but its magnitude was less as compared to the animals of experimental group. Exudate with protein deposits was accumulated in capsular spaces (Fig.2).

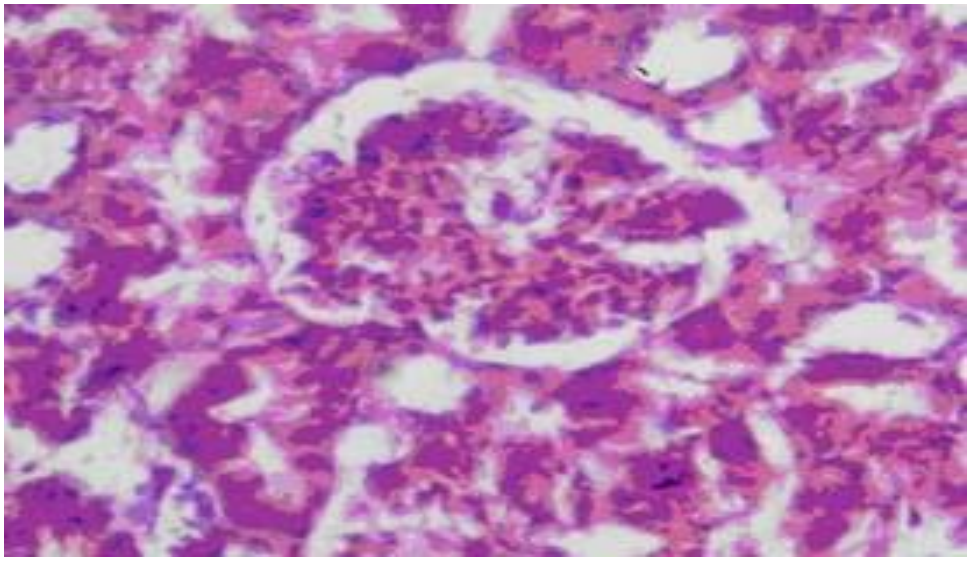

Fig.2. Structure of kidney glomerular component in toxic hepatitis in 90 days after L-arginine-L-glutamate correction. Staining with haematoxylin and eosin × 200.

After lisinopril correction moderate changes in glomerular component of kidneys were found being manifested by decreased capsular spaces, stabilized vascular structure (no signs of damage to endothelial cells, marked nuclei, good visualization of basement membranes). Blood filling of glomerular vessels remained uneven, capsular spaces were not dilated and contained no exudate (Fig.3).

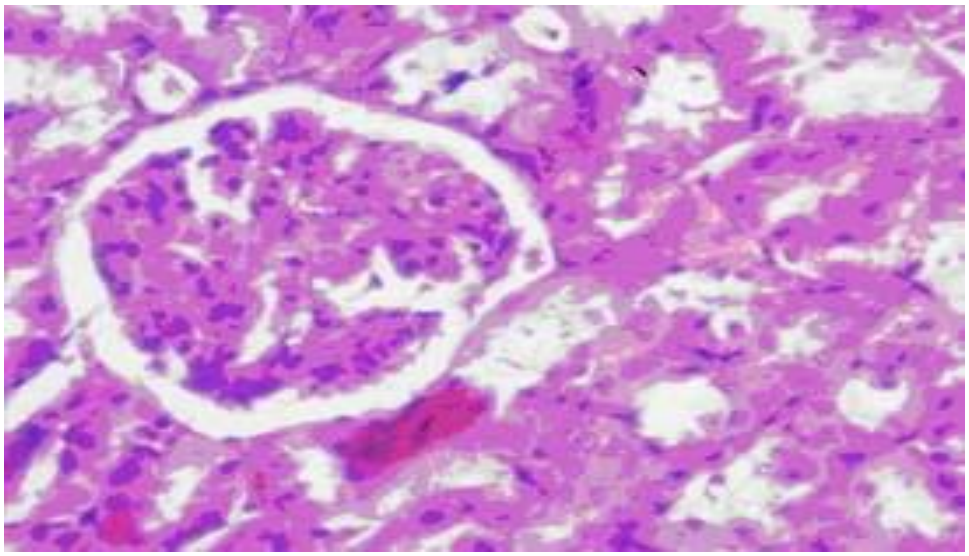

Fig.3. Structure of kidney glomerular component in toxic hepatitis in 90 days after lisinopril correction. Staining with haematoxylin and eosin × 200.

The most evident signs of lisinopril and L-arginine-L-glutamate correction were observed in renal cortex and medulla. Glomeruli were presented by vascular components with no marked morphological changes; capsular spaces were not dilated and contained no exudate. The vessels had normal structure but blood filling of glomerular vessels remained uneven (Fig.4).

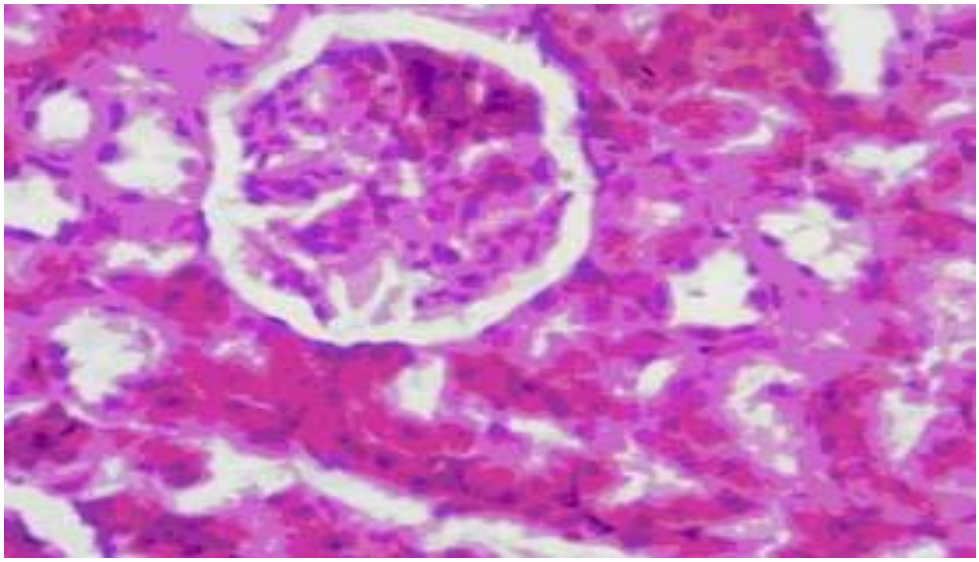

Fig.4. Structure of kidney glomerular component in toxic hepatitis in 90 days after lisinopril and L-arginine-L-glutamate correction. Staining with haematoxylin and eosin × 200.

Conclusions: Thus, it was found that after 90 days of experimental CTH in rats pronounced morphological changes developed in kidney glomeruli (vascular and cellular glomerular destruction). Use of drugs in the experiment decreased the magnitude of pathological changes. Administration of lisinopril contributed to restoration of glomerular structure. The use of L-arginine-L-glutamate was associated with decrease of dystrophic changes in kidney glomeruli. Combined use of both chemical compounds mutually potentiated their action and was accompanied by membrane-stabilizing effect and intensification of aforementioned restoration processes in structural components of nephron glomeruli.

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