СЕКЦІЯ 18
ФАРМАКОЛОГІЧНА ДІЯ ТА ФАРМАКОКІНЕТИКА ЛІКАРСЬКИХ ЗАСОБІВ

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THE NEPHROPROTECTIVE ACTIVITY OF GLUTATHIONE IN ACETAMINOPHEN-INDUCED ACUTE RENAL INJURY

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Acute kidney injury (AKI) has high rates of morbidity and mortality and is often accompanied with the development of multi-organ failure, which means that existing methods of its early diagnosis, prevention and management are not sufficiently effective. AKI is associated with an increased risk of mortality, cardiovascular events, and progression to chronic kidney disease. AKI occurs in approximately 10–15% of patients admitted to hospital, while its incidence in intensive care units has been reported in more than 50% of patients. This leads to an increase of 3% to 30% in mortality and additional costs. The mortality among patients who become dependent on dialysis during their hospital stay is drastically increased and lies between 14% and 41%. Acetaminophen (paracetamol) is one of the most widely used analgesic and antipyretic, however, an acute acetaminophen intoxication is associated with the hepatotoxicity and fulminant liver damage in 3-30% of cases. It is known that an acetaminophen overdose leads to the development of AKI in 3-14% of cases, and in some patients, the degree of damage to the kidneys does not correlate with the degree of liver injury. For this reason potent cytoprotector and antioxidant – glutathione has drawn our attention as remed for the pathogenetic correction of Acetaminophen - induce AKI. Glutathione is the most prevalent thiol-containing peptide in cells, what exerts multiple physiological functions including the proliferation, cell cycle regulation, catabolism of xenobiotics, glutathionylation of proteins, and the production of lipid compound, represents an important source of cysteine, possesses antitoxic and antioxidant effects.

The aim of research – to study a nephroprotective potential of Glutatione in conditions of Acetaminophen-induce AKI in rats. Research was conducted on 21 mature non-linear white rats weighting 130-180 g, randomly divided into 3 groups (n = 7): I group – intact control, II group – Acetaminophen-induce AKI (Acetaminophen-induced AKI was caused by a single intraperitoneal administration of acetaminophen (paracetamol, Health, Ukraine) at a dose of 750 mg/kg), rats of III group were daily administered with Glutatione (TAD 600, Biomedica Foscama, Italy) at a dose of 30 mg/kg, 1 h after paracetamol injection. Animals were withdrawn from the experiment 24 h after the last injection, while blood, urine were sampled for biochemical assessments.

Administration of the investigational drug in a therapeutic regimen resulted in a significant reduction of the degree of damage to nephrocytes in rats with Acetaminophen - induce AKI. Glutatione demonstrated hight nephroprotective efficacy, as evidenced by an improvement of the excretory kidney function with an increase in GFR by 2.5 times ($p<0,01$), diuresis – by 67.2% (p 0,01), reduction of azotemia and proteinuria. The protective effect of glutatione on epitheliocytes of proximal tubules is confirmed by an increase in reabsorption capacity and a corresponding decrease in fractional sodium excretion by 4.7 times ($p<0.01$), an increase in absolute reabsorption of sodium ions by 2.4 times ($p<0.01$), the maintenance of glomerular-tubular as well as normalization of tubular-tubular balance. At the same time, under the influence of glutatione an activation of the antioxidant defence (an increase in the antioxidant-prooxidant index in kidney tissue by 2.6 times ($p<0.01$)) and decrease in gamma-glutamyltranspeptidase activity in urine by 4.2 times ($p<0.01$) is observed, this evidences a cytoprotective effect correlating to morphological data.

Thus, glutatione produce a nephroprotective effect under the conditions of Acetaminophen-induce AKI and results may serve as a background for the further study under conditions of acute kidney injury of different etiology.