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NEPHROPROTECTIVE INFLUENCE OF ADEMETIONINE ON THE FUNCTIONAL STATE OF RATS KIDNEYS IN CONDITIONS OF GENTAMICIN-INDUCED KIDNEY INJURY

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Abstract

Nowadays acute kidney injury (AKI) is considered as an issue of increased global concern as its incidence is increasing over the years despite introduction of new therapies. Every 5th case of AKI is a result of toxic influence, including nephrotoxic effects of drugs. Nephrotoxicity is one of the most important side effects of aminoglycoside antibiotics, especially gentamicin, which causes kidney damage of different degree in 25% of patients. For this reason, there is a constant search for new therapies with nephroprotective activity, able to prevent or decrease toxic kidney injury during treatment with aminoglycosides. Functional state of kidneys in conditions of gentamicin-induced AKI and use of ademetionine was studied in an experiment on white male rats. Nephroprotective effect of ademetionine resulted in amelioration of excretory and ion-regulating kidney function of animals, confirmed by an increase in diuresis, glomerular filtration rate (GRF), reduction in

proteinuria, normalization of sodium and potassium balance. An established correlation between indices reflects restoration of functional activity of both proximal and distal parts of nephrons as well as maintenance of the kidney mechanisms of autoregulation. Obtained results justify further study of ademetionine as a promising nephroprotector.

Key words: acute kidney injury, nephroprotection, ademetionine, gentamicin

Taking into account the fact that AKI causes more than 2 million deaths over the world annually, search for new drugs with nephroprotective activity as well as investigation the renal effects of the existing drugs from different pharmacological groups is an area of active scientific interest [8, 3]. Quite often (about 30% of cases) AKI results from use of potentially nephrotoxic drugs [9]. Aminoglycoside antibiotics, especially gentamicin, are widely used in clinical practice due to their broad spectrum of antibacterial activity. A main disadvantage is its ability to accumulate in kidney cortex and cause damage to proximal tubular cells, which results in development of tubular dysfunction and necrosis of tubular epithelial cells [2, 5]. One of the main pathogenetic mechanisms of tubular damage progression is formation of active oxygen species and development of oxidative stress.

Ademetionine is an amino acid derivative, which possesses various effects such as antioxidant, membrane stabilizing, and regenerative [1, 7] It is clinically used as hepatoprotector with choleretic, cholekinetic and anti-cholestatic effects. [6, 10]

The aim of research was to study the possible nephroprotective activity of ademetionine on a model of gentamicin-induced AKI in rats.

Materials and methods

Research was conducted on 24 non-linear white male rate weighting 130-180 g, maintained under the standard vivarium conditions with a constant temperature and humidity, free access to water and food. Animals were randomly divided into 3 groups (n=7): I group – intact control, II group – gentamicin-induced AKI, III group – rats, which were administered with ademetionine («Abbott SpA», Italy) at a dose of 20 mg/kg. Ademetionine was injected intraperitoneally in a form of water solution 40 min after each gentamicin injection. Gentamicin-induced AKI was caused by single daily injection of 4% gentamicin sulfate solution («Galychfarm», Ukraine) at a dose of 80 mg/kg over 6 days [4]. Functional state of kidneys was evaluated on the 7^{th} day under the conditions of water load (intragastric administration of water (37ºC) in amount of 5% body weight). Rats were sacrificed, blood, urine and kidney samples were taken for analysis. Diuresis, glomerular filtration rate (GFR),

urine protein concentration and excretion, sodium and potassium excretion with urine were determined for evaluation of kidney function.

All studies were conducted in accordance with European Union Directive 2010/63/EU «On the protection of animals used for scientific purposes».

The results were processed using SPSS Statistics 17.0 software. The data distribution was determined using the Kolmogorov-Smirnov test. The differences between the samples were estimated using the Student's *t* test (in case of normal distribution) or nonparametric Mann-Whitney *U* test (when the distribution did not fit the normal law). The correlation between the variables was analyzed using Spearman's correlation coefficient (*r*). The minimum significance level was accepted at $p<0.05$.

Results and discussion

Obtained research results show a significant decrease in diuresis by 87.4% with simultaneous development of retention azotemia, confirmed by an increase of plasma creatinine level by 2.8 times, in II group of animals with AKI on the 7^{th} day of gentamicin administration (table 1). In the III group of animals (treated with ademetionine) there was an increase in diuresis by 75.5% and decrease in plasma creatinine level by 1.9 times comparing to II group of animals. GFR decreased by 3.2 times in II group along with a reduction of water reabsorption by 0.5%. Ademetionine administration caused an increase in GFR by 2.6 times, water reabsorption – 0.4%.

Degree of proteinuria in animals of II group significantly exceeded indices in control group: urine protein concentration increased in 4.5 times, protein excretion – by 2.4 times. Correction of pathology by ademetionine resulted in decrease in urine protein concentration by 2.7 times, protein excretion – by 1.5 times, compared to II group of animals. Direct toxic injury of proximal tubules by gentamicin resulted in reduction of their reabsorption capacity. Urine sodium concentration increased in 6.4 times, while its excretion increased in 3.4 times comparing to control. In group of rats which were injected with ademetionine sodium urine concentration significantly decreased by 3.5 times, excretion – by 2 times. Dynamics of absolute and relative sodium reabsorption indices indicates the ability of ademetionine to restore and maintain processes of filtration and reabsorption on kidneys, stimulating excretory kidney function. There was a significant reduction in absolute sodium reabsorption by 2.9 times, relative – by 6.7% comparing to control group. Under the influence of ademetionine absolute sodium reabsorption increased by 2.4 times, distal – by 4.7% comparing to II group of animals.

Table 1

Functional state of kidneys in conditions of gentamicin-induced AKI and administration of ademetionine, M±m (n=7)

Index	Control	Gentamicin-induced AKI	Gentamicin + Ademetionine
Diuresis, ml	4.63±0.19	2.47±0.10 $p_1<0.01$	4.34±0.11 $p_2<0.01$
GFR, µl/min	645.39±27.52	201.09±6.76 $p_1<0.01$	524.01±51.46 $p_2<0.01$
Plasma creatinine, µmol/l	43.49±1.01	121.88±3.40 $p_1<0.01$	64.06±3.95 $p_2<0.01$
Reabsorption of H_2O, %	99.28±0.01	98.77±0.05 $p_1<0.01$	99.14±0.07 $p_2<0.01$
Urine protein, g/l	0.017±0.002	0.076±0.006 $p_1<0.01$	0.028±0.003 $p_2<0.001$
Protein excretion, mg/100 µl	0.079±0.01	0.188±0.02 $p_1<0.01$	0.123±0.01 $p_2<0.01$
Urine Na, mmol/l	0.66±0.03	4.21±0.23 $p_1<0.01$	1.20±0.06 $p_2<0.01$
Na excretion, µmol/100 µl	3.09±0.21	10.47±0.70 $p_1<0.01$	5.21±0.31 $p_2<0.01$
Na absolute reabsorption, µmol /min	114.46±6.71	39.05±2.12 $p_1<0.01$	95.94±10.38 $p_2 \leq 0.01$
Na relative reabsorption, %	97.43±0.17	91.33±0.58 $p_1<0.01$	95.66±0.26 $p_2<0.01$
Proximal transport of Na, mmol/2 h	13.06±0.77	4.30±0.24 $p_1<0.01$	10.86±1.21 $p_2<0.01$
Distal transport of Na, µmol/2 h	679.29±33.73	390.01±21.87 $p_1<0.01$	654.86±37.17 $p_2<0.01$
Plasma K, µmol/l	5.14±0.25	4.24±0.26 $p_1<0.01$	5.21±0.49 $p_2<0.01$
K excretion, µmol/100 µl	4.19±0.12	20.60±1.19 $p_1<0.01$	9.11±0.93 $p_2<0.01$

Note. p_1 – in comparison with control, p_2 – in comparison with AKI

Processes of sodium transport were significantly affected in proximal as well as in the distal parts of nephrons. Both indices were normalized under the influence of ademetionine:

proximal sodium transport increased by 2.5 times, distal – by 1.7 times comparing to untreated animals.

Nephroprotective effect of ademetionine is confirmed by maintenance of renal autoregulation mechanisms: glomerular-tubular (correlation between GFR and transport of sodium in proximal (r=0.821) and distal parts of nephrons (r=0,857)) and tubular-tubular balance (correlation between proximal and distal sodium transport: r=-0,893).

Progression of gentamicin-induced AKI is usually accompanied by development of hypokalemia caused by injury of distal parts of nephrons. Potassium excretion with urine was significantly increased by 4.9 times in II group, which caused a reduction of plasma potassium concentration by 17.5%. Protective effect of ademetionine was realized in prevention of potassium loss: potassium excretion was decreased by 2.3 times, plasma potassium level remained on a control level.

Conclusion

Co-administration of ademetionine along with nephrotoxic gentamicin for 6 days prevented significant kidney injury. Nephroprotective effect of ademetionine is justified by the restoration of functional activity of tubular epitheliocytes. Obtained results have proved promise of ademetionine as a drug with nephroprotective activity and give a justification for the further study of its effects in conditions of AKI of different etiology.

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