Research Article

Nephroprotective Activity of Sodium Poly-(2,5-Dyhidroksyfenilen)-4-Thiosulfate acid Under Acute Renal Injury

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ABSTRACT

In the executed work nephro protective effect of PDT-Na is setted, which by most indicators exceed action of a reference drug thiotriazoline, manifested in conditions of experimental models of acute renal injury (ARI). According to mechanisms of kidney damage by applied models degree of protective action of PDT-Na in these conditions is different too: It turns out more in the background of the sample kidney damage by the type of crash-syndrome, which is evidence of renal antitoxic mechanism of its protection. Somewhat less this effect is manifested at gentamycin nephropathy, where is nephrotoxic factor accumulation gradually caused similar renal pathology and evidence of connection mechanism of PDT-Na with epithelium protective properties of the drug. Even less severe, but sufficiently, it is observed at the conditions of ethylene glycol model in which kidney disease combined with central nervous system disorders, and causes general antitoxic mechanism of nephroprotective PDT-Na action. In all models of ARI kidney protection is implemented by warning of enzymopathy development and normalization of blood electrolyte, which differ quantitatively. At the same time, common quality properties of PDT-Na, obviously, related to its nonspecific effects relating to anti-hypoxic and antioxidant actions which determine the direction of our further research.

Keywords: Acute kidney injury, nephroprotector, enzymopathy, electrolyte balance, antihypoxant.

INTRODUCTION

The pathology of kidney diseases in the structure of the WHO in recent years reaches a pandemic level. Regardless of the factors that trigger this pathology, it sometimes reaches 35.5 % of the visceral pathology and cause serious consequences and disability. Especially dangerous acute renal failure, in which the current aid is reached only through special equipment, enabling hemodialysis, an artificial kidney and organ transplantatiton. Modern farmacotherapy of kidney pathologies is mainly in the use of drugs of diuretic action, which, depending on the mechanism of diuretic impact does not always facilitate the kidney, and it may even worsen and weaken their excretory function[1-6]. Despite the fact, that most patients have recycling ARI, worldwide trend is to search for obvious clinically available diagnostic criteria for early kidney damage. As an auxiliary method of study, that reflects the morphological status of tubular epithelium, especially with employment of nephrotoxic drugs in treatment it is usage of enzymes activity research into the blood, so the determination of serum and urine can be used as a disease diagnosis method as well as for monitoring of therapy efficiency[7-10]. For the diagnosis of kidney damage it is recommended to determine the activity of enzymes that are localized mainly in the epithelium of the proximal segment of the nephron[11]. The key enzymes allowing to assessing the state of the nephron are lactate dehydrogenase (LDH), gamma glutamine transferase (GGT) and alkaline phosphatase (ALP).

General pathological processes, that occur under acute renal failure (impaired blood flow, vasoconstriction, ischemia tissue oxidative stress), determine the urgency of finding the necessary means of antihypoxants, antioxidants and other metabolic drugs. Given the above, it should be nephroprotective agent of polytropic action, that would have placed anti-hypoxic, antioxidant, membrane stabilizing, anti-inflammatory, desensitizing and diuretic effects. Some of them are peculiar to sodium poly-(2,5-dyhidroksyfenilen)-4-thiosulfate acid (PDT-Na), which improves tissue respiration under conditions of hypoxia, especially in organs with high metabolism, which include and kidneys; reduces the occurrence of toxic lipid peroxidation products, releases cells from metabolic products. The PDT-Na rapidly absorbed, what providing him efficiency under the acute pathology, and has a high degree of safety. However, the drug has not been studied as a nephroprotective agent and its research in the background of experimental renal pathology has a positive impact, preventing or slowing the pace of its development and possible chronic flow.

Medical efficiency of this drug in nephrology meet economic needs, limiting the use of high-cost drugs of substitution and symptomatic therapy. In turn, achieving economic efficiency will realize social needs, improving the quality of life of patients with kidney disease, increasing its durability, ability to work and be useful to the society.

MATERIALS AND METHODS

Experiments performed on 72 white mongrel mature nonlinear albino rats of both sexes weighing 150-170 g. Experiments were conducted in the laboratory of Department of Pharmacology and Prescription writing (Kharkiv National Medical University (KhNMU), Kharkiv, Ukraine).

All experiments were conducted according to the European convention for the protection of vertebrate animals used for experimental and other scientific purposes [Strasbourg, 1986] and according to the guidelines of the State Expert Center Ministry of Health of Ukraine (Protocol № 9 meeting of the Commission on Ethics and Bioethics KhNMU, 03.12.2014)[12-16].

According to the study of the design of PDT-Na nephroprotective activity for experimental ARI in terms of enzymopathy and electrolyte composition of blood used today, most informative model of acute toxic kidney damage of various origins: glycerol (mioglobinurical) ARI, ethylene glycol ARI and gentamycin nephropathy. These models reflect the basic pathogenesis of ARI, affordable and easy reproduced in laboratory conditions, suitable for screening and for in-depth studies of potential neuroprotective agents[17-29]. According to the study design, the experimental animals were divided into groups (by 6 rats): 1st group – intact control; 2nd group – pathology (under the experimental conditions); 3rd group – pathology + PDT-Na (90 mg/kg); 4th group – pathology + thiotriazoline (18 ml/kg). Doses determined according to the instructions for medical use of the considering a specific sensitivity factor according to Yu. R. Rybolovlev's method[30]. In the collected serum on the digital spectrophotometer PD-303 (Apel, Japan) according to the instructions used standard test set of reagents LLC Spain-lab (Kharkiv, Ukraine) in vitro determined activity of the main enzymes – morphological markers of kidney tubular epithelial condition of rats – LDH (pyruvate kinetic method), GGT (carboxylase kinetic method) and ALP (P-nitrophenilphosphate-kinetic method). The content of ions in the blood serum of rats was determined according to the instructions, using standard test kits reagents «Filisit diagnosis» (Dnepropetrovsk, Ukraine) – content of Na^+ ions (Mg-uranylacetate colometric method) and K^+ (turbo diametric method without deproteination).

Research results were processed by variation biomedical statistics methods using t-Student criteria by computer program «Statistica 6.0».

RESULTS AND DISCUSSION

Research of enzymopathies parameters in acute kidney injury

According to the obtained experimental data, presented in Table 1, revealed major changes in the concentration of marker enzymes, that indicate the presence of renal epithelial damage, during the ethylene glycol introduction to experimental rats. As can be seen from these results, the group pathology level of GGT, LDH and ALP during the study significantly increased in 1.44; 2.93 and 2.03 times, respectively, compared with intact control. This dynamic activity of the main enzymes testifies to the fact, that the application of ethylene glycol is rapidly developed renal pathology involving a cascade of biochemical reactions, including the development enzymopathy.

In the application of research drug – PDT-Na, activity of the studied enzymes GGT, LDH, ALP substantially normalize to the level of healthy animals. Thus, the concentration of GGT using PDT-Na is reduced by 30 %, LDH – 61 %, LF – 47 % for the group with pathology and has no significant difference with those values in the intact series (P> 0.05).

Table 1: Dynamics of enzyme activity in serum of rats with ethylene glycol ARI, n=6

The examined indicators	The experimental group of rats			
	Intact control M±m	Pathology M±m	Pathology+ PDT-Na M±m	Pathology+ thiotriazoline M±m
GGT (U/L)	46.81±3.67	67.63±3.25 *<0.01	47.20±4.49 *>0.05 **<0.05 ***>0.05	51.37±4.28 *>0.05 **<0.05
LDH (U/L)	11.16±0.96	32.75±1.79 *<0.001	12.81±1.28 *>0.05 **<0.001 ***<0.05	19.37±2.13 *<0.05 **<0.01
ALP (U/L)	22.17±1.08	45.10±3.97 *<0.01	23.85±1.94 *>0.05 **<0.01 ***>0.05	35.20±5.57 *>0.05 **>0.05

Notes: * - difference relating to intact control (p≤0.05);

** - difference relating to pathology (p≤0.05);

*** - difference relating to reference drug tiotriazoline (p≤0.05).

The fact that the concentration of the main enzymes (GGT, LDH, ALP) using investigational nephroprotective agent (PDT-Na) is lower than the levels, specified in the reference group «pathology + thiotriazoline» seems to be interesting too.

Thus, this study of PDT-Na impact on the dynamics of the main enzymes activity in the serum of rats with ethylen glycol ARI model allows to assert very clearly nephroprotective properties of potential nefroprotector, that is reflected in its ability to prevent and reduce the development of dangerous syndrom of acute nephropathy.

The influence of the sodium poly-(2,5-dyhidroksyfenilen)-4-thiosulfate acid on the level of serum enzymes in rats backgrounded in glycerol ARI indicates a similar trend, which is observed with the introduction of ethylene glycol. With these data in the Table 2 shows that the activity of enzymes (GGT, LDH and ALP) in serum of rats with experimental glycerol ARI rapidly and significantly increased during the study. Thus, the GGT concentration when administered glycerol in untreated ARI is significantly higher at 1.57 times compared with intact control. Levels of LDH and ALP in the background of glycerol ARI also higher than «normal» in 3.69 and 2.33 times, respectively. This dynamic of determined enzymes activity in the serum of rats with glycerol kidney damage (in terms of one of the most aggressive simulated pathologies) testifies to processes of membrane damage, occurring in nephrothelial kidneys and reducing the filtration capacity of the lattest under studied pathology.

Table 2: Dynamics of enzyme activity in serum of rats with glycerol ARI, n=6

The examined indicators	The experimental group of rats			
	Intact control M±m	Pathology M±m	Pathology+ PDT-Na M±m	Pathology+ thiotriazoline M±m
GGT (U / L)	46.81±3.67	73.38±3.40 *<0.01	50.58±3.08 *>0.05 **<0.05 ***>0.05	58.91±2.51 *<0.05 **<0.05
LDH (U/L)	11.16±0.96	41.21±1.71 *<0.001	14.45±0.95 *>0.05 **<0.001 ***<0.01	21.57±0.93 *<0.001 **<0.001
ALP (U/L)	22.17±1.08	51.70±2.51 *<0.001	25.96±1.32 *>0.05 **<0.001 ***<0.01	37.40±2.03 *<0.001 **<0.01

Notes: see. Table 1.

When used a study drug as a potential nephroprotective agent, we have shown that the concentration of GGT was significantly reduced by 31 % compared with pathology and brings the value of this enzyme similar to the «healthy» animals. LDH and ALP concentration in the blood serum of rats in the treatment of PDT-Na is also experiencing nature to normalize decreasing on average, almost 68 %, respectively, relative to the «sick» rats during the experiment. Also, decisive is that the application of PDT-Na activity of the studied enzymes in the serum of experimental rats, sometimes even is significantly lower than the value of similar reference drug (thiotriazoline).

The following snippet study, the dynamics of changes in the major enzymes (GGT, LDH, ALP) in the serum of rats with experimental reproduction of gentamycin nephropathy we have defined. During the study common changes in studied options of concentration with previous two studied models of ARI and introduction of gentamycin with nephrotoxic purpose was found out. Thus, activity of GGT (Table 3) in gentamycin introduction, again, as in the previous two studies was significantly increased by 23 % for indexes of intact control. The level of LDH at gentamycin nephropathy, also increased by 32 %, and the concentration of LF – 49 % compared to the intact series. In spite of such a nature activity of enzymes in the serum of experimental animals, we proved that it gentamycin nephropathy model is the least aggressive of the presented in this experiment. This may be explained by the lower toxic effect of gentamycin against the structures of the kidney, compared with ethylene glycol and glycerol.

Regarding of potential nephroprotective properties of the studied drug PDT-Na in conditions of gentamycin nephropathy, expressed his determined action aimed to reduce the level of GGT, LDH and ALP for research in 1.28; 2.58 and 1.77 times respectively compared with a series of «pathology».

As for the activity of the studied parameters in the application of the reference drug thiotriazoline at gentamycin nephropathy model, it is the highest level of GGT, LDH, ALP using PDT-Na. That is, nephroprotective action of reference drug is lower, than that, which is determined by using PDT-Na.

Thus, revealed dynamics of enzymes changes (GGT, LDH, ALP) in the serum of rats during the study and in all three models of ARI, evidence of their increase, and hence activation of membrane damage processes in nephron.

Table 3: Dynamics of enzyme activity in serum of rats with gentamycin ARI, n=6

The examined indicators	The experimental group of rats			
	Intact control M±m	Pathology M±m	Pathology+ PDT-Na M±m	Pathology+ thiotriazoline M±m
GGT (U / L)	46.81±3.67	61.09±1.91 *<0.05	47.80±3.41 *>0.05 **<0.05 ***>0.05	53.74±2.97 *>0.05 **>0.05
LDH (U/L)	11.16±0.96	34.48±1.80 *<0.001	13.38±1.14 *>0.05 **<0.001 ***<0.05	19.37±1.41 *<0.01 **<0.001
ALP (U/L)	22.17±1.08	45.10±2.78 *<0.001	25.47±1.62 *>0.05 **<0.001 ***<0.01	34.10±1.39 *<0.001 **<0.05

Notes: see. Table 1.

In health care administration the studied potential nefroprotective agent – PDT-Na in the background of ethylene glycol, glycerol ARI and gentamycin nephropathy pronounced its action aimed at preventing and / or reducing pathological signs in the tubules of the nephron, which in turn normalizes the level of the main enzymes (GGT, LDH, ALP) in the serum of experimental animals was proven.

Research of electrolyte metabolism in acute kidney injury

The next step is the actual research proved determine the concentration of Na^+ and K^+, as data electrolytes are involved in the regulation of homeostasis and is one of the most important elements in maintaining osmotic pressure of cells and the occurrence of an action potential. Based on this information, in this segment of our work dynamics of Na^+ and K^+ in serum of rats for three (ethylene glycol, glycerol and gentamycin) ARI models was defined.

From the above Table 4 data draws attention to the rapid significant increase level of serum sodium in rats with ethylene glycol kidney damage in 1.21 times relatively intact control. Similar dynamics is observed in determining of potassium concentration, which increases, when ethylene glycol used in untreated animals in about 1.28 times the corresponding values in the «healthy» rats. This trend to increase the studied serum electrolytes in animals with acute kidney damage in experimental conditions suggests possible violations in the filtration and renal excretory system. Also, this fact may explain our previous study, namely reducing the volume of daily urine output on the background of the being played pathology, consequently, decreasing sodium and potassium excretion in the urine and their accumulation in the blood.

As for the level of surveyed electrolytes (Na^+, K^+) in serum of rats with application of potential nephroprotective agent in reproduced pathology condition, the dynamics in lower concentrations to a «healthy» level was found. Based on the data presented in Table 4, the level of sodium and potassium in the PDT-Na application is reduced by 16 % and 19 %, respectively, as compared to the pathology and not reliable (P> 0,05) difference, that is defined in the intact group.

Table 4: Dynamics of sodium and potassium (mmol / L) level in blood serum of rats with ethylene glycol ARI, n=6

The examined indicators	The experimental group of rats			
	Intact control M±m	Pathology M±m	Pathology+ PDT-Na M±m	Pathology+ thiotriazoline M±m
Na^+ (mmol/l)	109.21±4.74	131.94±5.45 *<0.05	110.26±5.55 *>0.05 **<0.05 ***>0.05	112.37±2.98 *>0.05 **<0.01
K^+(mmol/l)	5.13±0.36	6.55±0.39 *<0.05	5.31±0.27 *>0.05 **<0.05 ***>0.05	5.51±0.29 *>0.05 ** >0.05

Notes: see. Table 1.

The study of therapeutic activity of potential nephroprotective agent – PDT-Na, the fact that the level of sodium and potassium in its application, even lower compared to the reference drug thiotriazoline we have proved. Thus, the Na+ concentration is lower when using PDT-Na by 2 % compared to thiotriazoline. Similar dynamics traced in determining the concentrations of K^+ (the level of which in the application of PDT-Na is lower by 3 % compared to thiotriazoline).

The next stage of this pilot study was to investigate the dynamics of Na^+ and K^+ concentration in serum of rats under the glycerol model, as the most toxic.

Table 5: Dynamics of sodium and potassium (mmol / L) level in blood serum of rats with glycerol ARI, n=6

The examined indicators	The experimental group of rats			
	Intact control M±m	Intact control M±m	Intact control M±m	Intact control M±m
Na^+ (mmol/l)	109.21±4.74	143.42±11.24 *<0.05	113.16±3.90 *>0.05 **<0.05 ***>0.05	114.21±3.21 *>0.05 **<0.05
K^+ (mmol/l)	5.13±0.36	7.29±0.34 *<0.01	5.55±0.28 *>0.05 **<0.01 ***>0.05	5.65±0.25 *>0.05 **<0.01

Notes: see. Table 1.

As can be seen from the following Table 5 results, the sodium and potassium concentration in the background of simulated glycerol ARI rapidly and significantly increased by 31 % and 42 %, respectively, compared with the series of intact control. Such dynamics change again allows us to emphasize the aggressiveness of the experimental ARI model.

In health care administration the studied potential nefroprotective agent – PDT-Na in the background of investigated pathology its ability to reduce (correct) in 1.27 and 1.31 times the Na^+ and K^+ level, respectively, compared with those defined in the pathology group was found. Also draws attention to the fact, that the activity of investigated potential nephroprotective agent (PDT-Na), again, is more pronounced relative to the reference drug (thiatriazoline), which is widely used for the treatment of nephropathy of different genesis.

At the last stage of this piece of the research, the activity of the electrolytes dynamics (Na^+, K^+) in the serum of rats under the experimental gentamycin ARI we have determined. Reported in the Table 6 rezults are indicate gentamycin nephrotoxicity action, as evidenced by increased of sodium and potassium level in the blood serum of the rats in the 1.14 and 1.29 times respectively compared to the «norm» during the experiment.

Table 6: Dynamics of sodium and potassium (mmol / L) level in blood serum of rats with gentamycin ARI, n=6

The examined indicators	The experimental group of rats			
	Intact control M±m	Intact control M±m	Intact control M±m	Intact control M±m
Na^+ (mmol/l)	109.21±4.74	125.00±4.28 *<0.05	111.84±3.17 *>0.05 **<0.05 ***>0.05	113,42±2,46 *>0.05 **>0.05
K^+ (mmol/l)	5.13±0.36	6.64±0.49 *<0.05	5,31±0.31 *>0.05 **>0.05 ***>0.05	5.48±0.19 *>0.05 **>0.05

Notes: see. Table 1.

In the application of PDT-Na concentration of the studied electrolytes (sodium, potassium) was significantly reduced by 11 % and 20 %, respectively, regarding similar series of «pathology» and has no significant difference (P> 0.05) with intact level. Also revealed the fact, that studying nefroprotective agent more clearly eliminates hypernatremia and hyperkalemia than the reference drug – thiatriazoline.

CONCLUSION

Thus, in all experimental models of ARI renal protection realized by warning enzymopathy development and normalization of blood electrolyte composition, what characterized quantitatively. These potential nephroprotective properties of PDT-Na, obviously, related to its nonspecific effects, such as anti-hypoxic and antioxidant actions, which determine the direction of our further research.

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