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INDOLINOREN EFFECT ON THE EXPERIMENTAL ACUTE RENAL FAILURE

SUMMARY

There are results of the study of impact of indolinoren on experimental acute renal failure on rats provided in this work. Was established that investigated substance indolinoren promotes diuresis and has protective properties on nefron, as evidenced by the reduction of proteinuria and preventing anuria.

Key words: indolinoren, acute renal failure, diuretic activity.

Acute renal failure (ARF) is one of the most dangerous emergency conditions [3, 11]. Currently in the general population incidence of acute renal failure is close to 200 per 1 million of population, and it occurs 5 times more frequently in elderly people than in young people. Gross violations of water-electrolyte and nitrogen metabolism in ARF lead to functions' disorder of all vital organs and systems: cardiovascular, nervous, respiratory, liver [1, 9]. ARF can be caused by infection, hypovolemia, heart failure, and nephrotoxins such as aminoglycoside antibiotics. Despite improved methods of prevention and treatment, the mortality rate from ARF remains consistently high over the past 10 years. Chronic pathologic process in kidneys is often irreversible. It is known that ARF with the absence of oliguria has better prognosis than ARF with severe oliguria [8]. Because oliguria is very significant risk factor for ARF, high doses of diuretics are included in the regimen of ARF treatment very often in order to increase urine output and transition of oliguric ARF in neolihurychn [7, 10].

The aim of our work was to study the effect indolinoren that preliminary showed a pronounced diuretic effect on the state of renal excretory function in rats with experimental ARF.

Materials and methods. ARF was reproduced by intramuscular introduction of 50% glycerol solution at a dose of 10 ml / kg to test animals one time [6]. This model is one of the best investigated. Important factors of the pathogenesis of this ARF model are ischemia of the kidneys, reduced renal blood flow, that caused by hypovolemia - a consequence of osmotic action of glycerol. Experiments were performed on 40 white nonlinear rats-females weighing 180-220 g, that were on a standard diet of food and water according to sanitary norms [5]. During the experiment animals were treated according to international principles "of the European Convention for the Protection of vertebrate animals used for experimental and other scientific purposes" (Strasbourg, 18.03.1986) and "General ethical principles of animal research" (Ukraine, 2001). Experimental animals were divided into 4 groups: 1st group - intact control, 2nd group - rats with ARF without treatment, 3rd - rats with ARF injected with indolinoren, and 4 - rats with ARF, they were administered comparative drug. In this study, diuretic furosemide was chosen as comparative drug (manufactured by PJSC SIC "Borshchahivskiy CPP", Ukraine). This diuretic is commonly included in treatment regimens for ARF [7]. Indolinoren and furosemide were administered intragastric in health-care mode for 3 days before modeling of ARF and for 2 days when ARF had already been developed. Investigated compound and comparative drug were administered in effective doses of 29.5 mg / kg and 6 mg / kg, respectively. Efficiency of indolinoren was defined according to measurement of renal excretory function on the first and second day of ARF, according to biochemical indicators of urine and serum on the second day of ARF. The content of creatinine in plasma and urine was determined by the Jaffe reaction, urea - by the reaction with diazetylmonooxym using standard kits PNP "Filisit-Diagnosis" (Ukraine), the concentration of protein in the urine – by the reaction with sulphosalicylic acid [2].

Obtained results were processed with approved methods of variation statistics with Student's t criterion using software «Windows-XP», Excel spreadsheets [4].

Results and discussion.

The results obtained in the experiment showed that in conditions of acute toxic kidney damage animals of the control group had a significant disorder of renal excretory function. In conditions of water stress control group had a significant change in rates compared with intact group of animals. Oligoanuric stage of ARF was observed, anuria occurred in 20% of cases on the 2nd day of experiment and in 60% of cases - on the 3rd day. Diuresis in rats of control group to animals of intact group on the 2nd day of the experiment was $0,55 \pm 0,10$ ml/100 g (for rats without anuria), on the 3rd day - $0,26 \pm 0,05$ ml/100 g (for rats without anuria) (Table 1).

Table 1

Impact of indolinoren on diuresis in rats with ARF in terms water stress (

$$\bar{X} \pm S\bar{x}, n=10)$$

Conditions of experiment	Diuresis, ml/100 g during 3 hours	
	2 day of experiment	3 day of experiment
Intact control	$2,54 \pm 0,10$	$2,55 \pm 0,22$
Control group (ARF)	$\frac{0,44 \pm 0,11 *}{0,55 \pm 0,10 *}$	$\frac{0,10 \pm 0,04 *}{0,26 \pm 0,05 *}$
ARF + Indolinoren	$1,74 \pm 0,14 */**/**$	$\frac{1,23 \pm 0,27 */**}{1,53 \pm 0,22 */**}$
ARF +Furocemide	$2,19 \pm 0,11 */**$	$\frac{1,60 \pm 0,33 */**}{2,0 \pm 0,24 */**}$

Notes:

In the numerator - an indicator for the whole group and in the denominator - for animals without anuria.

1. * - $p < 0.05$ relative to intact control;
2. ** - $p < 0.05$ relative to control;
3. *** - $p < 0.05$ relative to furosemide.

The result of the experiment revealed that the studied compound - indolinoren significantly increased the diuresis in terms of ARF: the 2nd day diuresis was - $1,74 \pm 0,14$ ml/100 g, which is almost 4 times more compared with the control group of animals (Table .1). On the 3rd day of the experiment diuresis slightly decreased and

was $1,23 \pm 0,27$ for the whole group of animals and $1,53 \pm 0,22$ - for animals without anuria. Anuria was present in 20% of animals.

It was found that during the experiment indolinoren was inferior to comparative medicine - furosemide on the 2nd day of the experiment and had no significant difference on the 3rd day.

Indicators severe flow model pathology are also significant increase in blood creatinine - 2.9 times, decrease of urine creatinine in 1.1 times, increasing of concentrations of urea in blood in 6.8 times and reducing of the amount of urea in urine 1.6 times in control group of animals relative to intact rats (Table 2). Significant proteinuria was marked on the 3rd day. Thus, the concentration of protein in the urine of control group rats increased in 4.25 times compared with intact group of animals (Table 2). Findings testify against the state of "shock" kidney in animals of the control group.

Table 2

Impact of indolinoren on biochemical parameters of blood serum and urine of rats with ARF ($\bar{X} \pm S\bar{x}$, n=10)

Indicator	Conditions of experiment			
	Intact control	Control group (ARF)	ARF + Indolinoren	ARF +Furocemide
Creatinine in urine, mmol/L	1,02±0,02	0,91±0,01*	2,39±0,55*/**	1,67±0,22*/**
Creatinine in blood serum, mmol/L	0,11±0,01	0,32±0,01*	0,16±0,01*/**	0,13±0,01**
Urea in urine, mmol/L	261,82±19,93	165,95±13,79*	222,97±21,99**	242,59±22,96**

Urea in сироватки крові, mmol/L	4,05±0,40	27,49±1,56*	9,19±1,01*/**	7,29±0,33*/**
Protein in urine, g/l	0,04±0,01	0,17±0,02*	0,10±0,01*/**/**	0,06±0,01**

Notes:

1. * - $p < 0.05$ relative to intact control;
2. ** - $p < 0.05$ relative to control;
3. *** - $p < 0.05$ relative to furosemide.

It was established during the experiment that indolinoren reduces serum creatinine in 2 times, and increases urine creatinine in 2.6 times compared to animals of control group. The level of urea in animal urine, to whom indolinoren was administered, in 1.3 times was lower relative to the control group of animals and by its meaning was close to intact group of animals (Table 2). The result of the experiment revealed that indolinoren reduces the amount of protein in urine in 1.7 times compared with the control group of animals. Comparative drug - furosemide relatively to investigated indicators in blood and urine has slightly superior effect than indolinoren, but has no significant difference, except for urine protein level. Thus, in group of animals, which was administered furosemide, it was observed the reduction of serum creatinine in 2.5 times and the increase of urine creatinine in 1.8 times, decrease of urine protein in 2.8 times compared with the control group.

Conclusions

1. Investigated substance indolinoren in effective dose of 29.5 mg / kg on the model of ARF promotes diuresis and has pronounced renalprotective properties. Decreasing of proteinuria and anuria prevention testify to this fact.
2. Results indicate the appropriateness of further deep study of indolinoren as a promising diuretic for treatment of ARF.

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