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Research Article

Efficacy Of 6-Hydroxy-*N*-(4-Methoxyphenyl)-4-Oxo-1,2-Dihydro-4*H* Pyrrolo[3,2,1-*ij*]Quinoline-5-Carboxamide In Modeling Renal Insufficiency

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Abstract

Kidney failure is a severe consequence of chronic kidney diseases, which is accompanied by disorder of kidneys' homeostatic function with development of azotemia, violations of water-electrolyte metabolism and acid-base status with diseases accession, such as anemia, hypertension, and so on. As a result of circulatory disorders in the kidneys, that leads to a delay products in blood which are normally excreted in the urine, the pathological process raises that reflected in the inability of all or most of the nephrons of the kidney to maintain homeostasis - acute renal failure. Taking into consideration the steady trend to the quantity rise of kidney diseases and despite improving the modern methods of prevention and treatment, search for new effective nephroprotective medicines is actual issue. Accordingly, the aim of this work was a research of specific pharmacological activity of substance 6-hydroxy-*N*-(4-metoxyphenyl)-4-oxo-1,2-dihydro-4*H*-pyrrolo[3,2, 1-*ij*]quinoline-5-carboxamide on a model of renal failure. For toxic nephrosis-nephritis modeling, the ethylene glycol was applied by intragastrically administration to rats once in a dosage of 2.5 g / kg, since it is known that it causes classic kidney damage with renal failure and oliguria syndrome. Study of the substance effectiveness was evaluated according to its diuretic action and results of the experimental animals urine analysis. It was established that the stated substance has practically normalized the indices, such as value of pH, protein and urine solidity. The obtained results demonstrate that the substance renews the kidneys' function while serious nephrosis-nephritis, caused by ethylene glycol and has a diuretic action.

Keywords: *Substance, Quinoline-carboxylic acids, Renal insufficiency, Homeostasis, Diuretic action*

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Introduction

It is known that kidneys accomplish the function of body purification – removal of waste, toxins and byproducts. Abnormalities in kidney functions lead to accumulation of harmful substances in a body, intoxication. Consequence of a chronic renal disease is a renal insufficiency - disorder of kidneys homeostatic function with azotemia development, violation of water- electrolyte and acid -base status accompanied with anemia, osteopathy, arterial hypertension, and immunodeficiency states.

As a result of impaired circulation in kidneys and products retention in blood normally excreted from a body with urine, a polyetiological process occurs such as an acute renal insufficiency (ARI).

ARI is a potentially reverse pathological process which is expressed as a failure of all or the most part of kidney nephrons to maintain homeostasis. Usually, one of the first symptoms of an acute renal insufficiency is considered to be a reduction or cessation of urine secretion. Herewith, an oliguria is distinguished when daily urine output is less than 0.2 mL / kg /h and an anuria when diuresis is less than 0.05 mL / kg / h for adult patients. Often ARI is just one of the components of several organs failure and is countable as a syndrome of multi-organ dysfunction that has an adverse impact on survival [1, 2].

Despite improvement of the methods of prevention and treatment, including dialysis, a level of mortality associated with ARI reaches 50%, a search for new effective nephroprotective drugs is a topical issue [3]. A substance of 6-hydroxy-N-(4-methoxyphenyl)-4-oxo-1,2-dihydro-4H-pyrro-lo[3,2,1-ij]quinoline-5-carboxamide was synthesized at the Pharmaceutical Chemistry department of the National University of Pharmacy (Figure). In practice, this compound is non-toxic one and exhibits a significant diuretic activity [4].

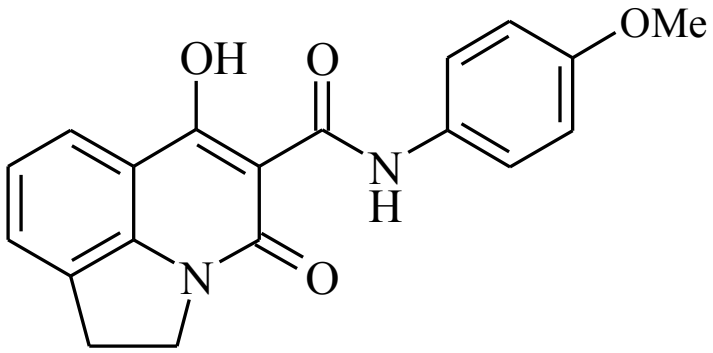

Figure 1. Chemical structure of compound 6-hydroxy-*N*-(4-methoxyphenyl)-4-oxo-1,2-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline-5-carboxamide

The aim of this work was to study specific pharmacological activity of the substance of 6-hydroxy-N-(4-methoxyphenyl)-4-oxo-1,2-dihydro-4*H*-pyrrol[3,2,1-*ij*]quinolin-5-carboxamide on a model of renal insufficiency.

Experimental

Materials and Methods

The study was conducted on the nonlinear white male rats of a standard weight 160-170 g. For the toxic nephrosis-nephritis modeling, an ethylene glycol was intragastrically administered to rats one time in a dosage of 2.5 g / kg through metallic atraumatic probe [5]. The ethylene glycol was offered because it causes classical kidney damage with a renal failure and oliguric syndrome. The substance of 6-hydroxy-*N*-(4-methoxyphenyl)-4-oxo-1,2-dihydro-4*H*-pyrro-lo[3,2,1-*ij*]quinoline-5-carboxamide were intragastrically injected on the 2nd day in a dosage of 10 mg/kg twice a day for three-days period.

Totally, three experimental groups were formed (each experimental group consisted of 10 animals): *1 group* – intact animals; *2 group* – treatment-free intoxicated animals; *3 group* – intoxicated animals with treatment by the substance of 6-hydroxy-*N*-(4- methoxyphenyl)-4-oxo-1,2-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline-5-carboxamide.

In order to collect daily urine, experimental animals were placed into metabolism cages by Italian company «Texnoplast». An analysis of the urine collected was carried out by generally accepted methods [6]. All studies on animals were conducted in accordance with the Directive of the European Parliament and Union 2010/63 EU on the protection of vertebrate animals used for experimental and other scientific purposes dd. from 22.09.2010.

Statistic processing of the experimental data was performed by means of a package of electronic Excel tables for statistical analysis [7] and the program "Statgraphics Plus v. 3.0". The average values of indices (x) and standard error (Sx) were calculated. A probability of differences between the averages was determined by Student-Fisher's criteria [8]. A probability of the results obtained was estimated at a level of significance at least 95% ($p \leq 0,05$).

Results and Discussion

Efficacy of the substance of 6-hydroxy-*N*-(4-methoxyphenyl)-4-oxo-1,2-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline-5-carboxamide was evaluated by diuretic action and on the basis of urine test results of the experimental animals (**Table 1)** [9].

Table 1 Volume of drank water, daily urine and urine analysis of experimental animals intoxicated by an ethylenglycol and treated by the substance in a dosage of 0.5 ml/kg, (M±m, n=10)

Experimental groups	Daily urine, ml	Volume of drank water, ml/day	pH of urine	Protein of urine, mg/ml	Urine spissitude, g/ml
Intact	3.6 ±0.1	18±3	6.5±0.5	4.7 ± 0.5	1.016±0.002
Treatment-free	1.6 ± 0.2*	28±5*	8.5±0.2*	12.0±1.1*	1.006±0.003*
Substance	3.1 ± 0.2	16±2	6.6±0.2	5.7 ± 0.4	1.014±0.002

*reliable difference from intact animals at $p < 0.05$

In a group of treatment-free animals there was a violation of kidneys' concentrative function (oliguria, alkaline urine, decrease of a specific gravity). Additionally, the violation of kidneys' filtration function was revealed (increase of urine protein value). At the end of observation, three animals from the treatment-free group have died.

While administration of the substance of 6-hydroxy-N-(4-methoxyphenyl)-4-oxo-1,2-dihydro-4*H*-pyrrol[3,2,1-*ij*]quinoline-5-carboxamide in the third group of animal, improvement was observed of the animals general state and of kidneys functions. None of treated animals have died. It was defined that the stated substance normalized in practice such indices as values of pH, protein and urine spissitude. The obtained results have shown that the 6-hydroxy-N-(4- methoxyphenyl)-4-oxo-1,2-dihydro-4*H*-pyrrol[3,2,1-*ij*]quinolin-5-carboxamid renovates kidneys function while severe nephrosis-nephritis caused by ethylenglycol, and has a diuretic action.

Conclusions

The effectiveness of substance 6-hydroxy-N-(4-metoxyphenyl)-4-oxo-1,2-dihydro-4H-pyrrolo[3,2,1-ij]quinoline-5-carboxamid was demonstrated, that normalizes indices of renal homeostasis. It was proved that the analyzed substance creates diuretic action and renews kidneys' function while acute renal failure modeling.

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