

HISTOMORPHOLOGICAL CHANGES IN THE KIDNEYS IN CASE OF CLOZAPINE POISONING

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INTRODUCTION

Poisoning is one of the most important issues of forensic medicine. Clozapine is an example of so called *atypical* neuroleptics [1]. The therapeutic threshold of this drug is comparatively narrow. A single therapeutic dose of this drug is 50–200 mg, the highest daily dose is 900 mg., whereas a fatal dose for an adult is about 2 g [2]. Clozapine is widely used in clinical practice to treat acute and chronic forms of schizophrenia, psychosis, manic conditions, bipolar disorders, aggressiveness and others [3]. More than one million people in more than 60 countries of the world undergo treatment with clozapine annually. All the facts mentioned above determine a high risk of clozapine poisoning. The number of criminal clozapine intoxications in Russia also remains high. Such poisonings are characterized by severe symptoms and high mortality.

The objectives of the study:

to estimate in the experiments on laboratory rats histomorphological changes in the kidneys in acute clozapine poisonings 3 and 24 hours after the intoxication.

MATERIALS AND METHODS

We performed a comparative study of histological sections of the kidneys of outbreed male rats weighing 290–350 g. Group 1 and 2 included 5 rats treated with clozapine oral dose (150 mg/kg) and euthanized 3 and 24 hours after drug administration, respectively. Control group included 5 intact rats. The concentration of clozapine and its main metabolites was measured using high performance liquid chromatography method with mass spectrograph detection (HPLC-MS/MS) method.

RESULTS

No pathological changes were detected in the group of comparison. 3 hours after clozapine administration a slight expansion of the lumen of the capsules was detected in the glomeruli of the kidneys. The nuclei of some epithelial cells of the convoluted tubule of kidneys were not stained. There were some visible small vacuoles in the cytoplasm. Venous plethora was observed. The tubules of the medullary area were moderately dilated. The nuclei of epithelial cells of the tubules of the medullary area were round, mainly normochromic. There were cells with hyperchromic and hypochromic nuclei. There were small hemorrhages in the cortical layer.

Some protein was present in the tubules. 24 hours after the clozapine administration the nuclei of the cells were not stained. There was protein in the lumen of the tubules. On the border of the medullary area and medullary layer the vessels were moderately full-blooded, focal hemorrhages are observed. Some tubules in the brain layer are expanded. In case of treatment with clozapine the clozapine and the norclozapine concentration in kidney homogenate was 2,8 times higher and 5 times lower as compared with 3 hours, respectively. The concentration of clozapine-N-oxide slightly decreased.

CONCLUSION

In case of clozapine poisoning, a complex of severe morphological changes in the kidneys was observed. These signs along with the results of histological studies of other internal organs and chemical studies and can be used to evaluate the severity of the intoxication and the exact time of the poisonings.

REFERENCES

1. Clozaril (clozapine tablets) [product monograph] Dorval (QC): Novartis Pharmaceuticals Canada Inc; 2014. Aug 19.
2. FLANAGAN R.J. Fatal toxicity of drugs used in psychiatry. *Hum. Psychopharmacol.* 2008; 23 (Suppl 1): 43–51. DOI: 10.1002/hup.916
3. GREEN A., TOHEN M., PATEL J.K., BANOV M., DURAND C., BERMAN I., CHANG H., ZARATE C., POSENER J., LEE H., DAWSON R., RICHARDS C., COLE J.O., SCHATZBERG A.F. Clozapine in the treatment of refractory psychotic mania. *Am. J. Psychiatry.* 2000; 157 (6): 982–986. DOI: 10.1176/appi.ajp.157.6.982.