NONANTIBIOTIC PROPERTIES OF TETRACYCLINES

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Tetracycline antibiotics include a number of drugs related in chemical structure, antimicrobial spectrum and mechanism of action, the features of which still continue to be refined. Among the new applications of tetracyclines is their widely use as a tools for studying the mechanisms of disorders of the various structures of the body, as well as to develop the new approaches to the use of these drugs in the diagnostics and treatment of various human diseases, such as rheumatoid arthritis and other systemic diseases. Currently one of the rapidly developing areas of researches is the study of immunomodulatory and anti-inflammatory effects of antibiotics. While studying the effects of tetracyclines in the therapy of noncommunicable diseases, particularly in the treatment of immune and skin diseases, some authors have been concluded that the therapeutic action of this drugs is realized due to the influence on immune system. Nonantimicrobial effects of tetracyclines also includes pro-apoptotic, anti-tumor, neuroprotective, genotropic and other effects on the macroorganism.

Tetracyclines – a relatively low toxic substances, but long-term use leads to the development of side effects of varying severity. One of the possible way to improve the safety of this group is to create combined drugs containing tetracycline antibiotics and biologically active substances that modify their toxic properties.

The tasks of this study were to conduct the comparative analysis of safety as well as finding the median lethal dose (LD_{50}) of tetracycline hydrochloride, doxycycline hydrochloride, methacycline hydrochloride and to determine the optimal remedy for the further studies as anti-inflammatory and chondroprotective drug.

Materials and Methods. A study of acute toxicity of the oral forms of tetracycline hydrochloride, doxycycline hydrochloride, methacycline hydrochloride were conducted according to the V.B. Prozorovsky method in 108 white outbred rats of both genders with the body weight 180.0-200.0 g divided into three series of 6 groups, there were 6 animals in each group. Animals of experimental groups received tetracycline hydrochloride, doxycycline hydrochloride, methacycline hydrochloride in doses ranging from 500 mg/kg to 5000 mg/kg. Drugs were administered intragastrically in appropriate doses dissolving them in the necessary amount of saline solution. For the calculation of the median lethal dose (LD_{50}) was determined the percentage of mortality in each group after 14 days. Using tables and calculations

in accordance with the V.B. Prozorovsky method of probit-analysis of the curves of lethality the value of LD_{50} was determined.

Results. The observation of the animals has been carried out within two weeks after drug administration. Already on the second day after drug administration in groups of rats used doxycycline in doses 2000 – 5000 mg/kg the first fatal cases were observed. At the end of the first week a certain level of lethality has been observed in all groups, except the group of rats used the drug in the dose 500 mg/kg. Then the average mortality rate reached its maximum at 8-9 days of the experiment. The median lethal dose was calculated based on the activity of the drug depending on the applied dose by probit-analysis. Using the tabular data the percentage of mortality in each group were transferred into probits and then the weight coefficients and place of doses were determined carrying out further necessary calculations. According to experimental data was plotted the graph of probit analysis of the dependence "dose-mortality".

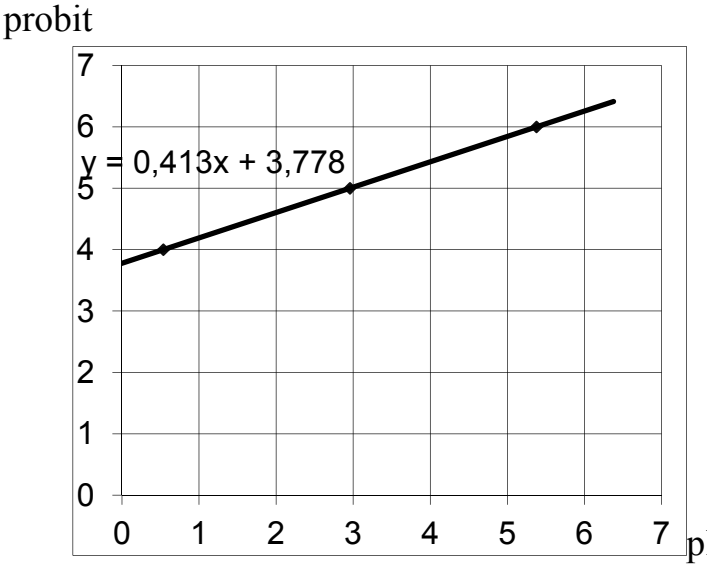

Figure 1. Graph of the probit analysis of dependence "dose-lethality" of the tetracycline

Conclusion. 1. The results of the conducted investigations and calculations lead to the conclusion that the LD_{50} level of tetracycline hydrochloride after single oral administration in rats is 1478.22±201.67 mg/kg; LD_{50} of doxycycline hydrochloride – 1893.03±286.2 mg/kg; LD_{50} of methacycline hydrochloride – 1635.73±199.36 mg/kg. Thus, doxycycline is significantly safer than tetracycline and methacycline.

2. The obtained results allow to refer the studied drugs to the IV class of toxicity – the low toxic substances according to the standard K. K. Sidorov classification.

3. It is recommended to carry out the further studies of the mechanisms of anti-inflammatory and possible anti-rheumatic effects of tetracyclines and their combinations with potential anti-inflammatory and chondroprotective substances.