



Acute Toxicity of The Pharmaceutical Substance Branched Oligohexamethyleneguanidine Hydrochloride at Mice and Rats after Intragastric Administration

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Abstract

The toxicity of pharmaceutical substances remains one of the main issues of modern research. Accordingly, the search for analogues with lowered toxicity as compared to established substances remains a major task for modern pharmacology. A promising compound in this respect is OHMG-HCl, the toxicity of which is examined in this study. The results of the study indicate that the application of OHMG- HCl to be a promising perspective due to its low toxicity.

Keywords: Toxicity; Toxicology; OHMG-HCl; Branched oligohexamethyleneguanidine hydrochloride; Acute toxicity.

Abbreviations: OHMG-HCl: Oligohexamethyleneguanidine Hydrochloride; JSC: Joint-Stock Company

Introduction

The excipient OHMG-HCl is a branched oligohexamethyleneguanidine hydrochloride and also is a synthetic high molecular weight derivative of guanidine [1-3]. Currently, the promising substances are poly guanidines-synthetic high-molecular derivatives of a specific nitrogen base-guanidine. Distributed in nature, have high efficiency and long-term biocidal effect, so that poly guanidines are widely used in agriculture as preservatives for seeds of agricultural plants, in medicine and veterinary medicine as antimicrobial drugs [4-8]. Due to their wide spectrum of antimicrobial activity combined with low toxicity, guanidine derivatives are already for a long time established as active substances in many antiseptics. Drugs based on polyhexamethylene guanidium salts keep in their activity in a wide range of environmental conditions, easy solve in a water and prevent the formation of microbial biofilms [1,9,10].

The mechanism of the antimicrobial action of polyguanidines is based on the destruction of ester bonds in the lipids and

lipopolysaccharide complexes of microbial cell membranes, which initially leads to the repression of aggression factors (plasmaoagulases, hyaluronidase, oxidation of SH-groups of glycolytic enzymes) and forthcoming death of infectious agents [9]. Polyguanidines are able to sharp movement to the surface of the bacterial cell due to electrostatic interactions and then disturb its integrity by replacing of metal cations [9,10]. Due to the widespread development of antibiotic resistance among microorganisms, the antiseptic drugs are particular importance for the treatment of ubiquitous acute and chronic infections of the oral cavity and throat, such as tonsillitis, pharyngitis, laryngitis and periodontal diseases [11]. Among the most common pathogens of the aerobic microbiota are *Streptococcus* spp, *H. influenzae*, *M. catarrhalis*, *S. aureus*, *N. gonorrhoeae*, *Candida* spp [4,10,12]. It is believed that OHMG-HCl, as other polyguanidines, has a low level of toxicity in comparing with non- branched oligohexamethylene guanidine hydrochloride. Accordingly, the objective of this study is to detect acute toxicity and determine the toxicity class.

Materials and Methods

Chemicals

The studied compound is the pharmaceutical substance "branched oligohexamethylene guanidine hydrochloride" (produced in JSC «Institute of Pharmaceutical Technologies» (IPT), Russia).

Test system

The realization of the established objective was only possible with the use of experimental animals, since animal research provides the most complete data on the toxicity of a given drug. In toxicological research the standard subjects are mice and rats. The experiment was performed on outbred mice (males and females) with a starting weight of 25-30 g and on outbred rats, with a starting weight of 300-350 g for males and 210-260 g for females. Each animal was designated with an individual paint mark. The animals were selected and divided into groups by weight and age so that the mass of each animal would not deviate from the group average by more than 20%. All actions with the animals were performed according to the rules of the European Convention for the Protection of Vertebrate Animals Used for Experimental and other Scientific Purposes (ETS 123) Strasbourg, 1986.

Method of administration, choice of doses, and drug preparation for administration

During the study was used method of intragastric administration, to study the substance's toxicity in systemic application. In a preliminary test on both mice and rats the animals received intragastric doses of 5 mg/kg, 200 mg/kg, and 800 mg/kg. Animal death was established at the 800 mg/kg dose. Accordingly, in the main experiment the administered doses amounted to 200 mg/kg, 400 mg/kg, 600 mg/kg, and 800 mg/kg.

Results and Discussion

This study on the acute toxicity of branched oligohexamethyleneguanidine hydrochloride performed on outbred mice and rats of both sexes showed that upon one-time intragastric administration the substance has a dose-dependent toxic effect to the animal. The median lethal dose amounted to 417 mg/kg for male mice, 490 mg/kg for female mice, 501 mg/kg for male rats, and 457 mg/kg for female rats. In the case of mice it was noticed the influence of subtoxic doses of the studied substance on body weight mass decreasing. However, upon autopsy there were no observed remaining signs of intoxication or pathological changes in the structures of internal organs. Morphometric analysis showed decreasing of the relative weight of the thymus and spleen.

Female rats receiving a dose of 400 mg/kg showed the increasing of the relative weight of the liver and brain.

Conclusion

Based on obtained data the studied substance was attributed to the IV class of the low toxicity substance (301 – 2000 mg/kg in intragastric administration) (Classes of toxicity of substances in accordance with the modified classification of the Organization for Economic Cooperation and Development).

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