The Research of Abnormal Toxicity and Local Irritant Effect in the Draize Test of the Drug Furacilin, Concentrate for the Preparation of a Solution for Local and External Use

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Abstract

Introduction: The research of abnormal toxicity and locally irritating effect of the drug Furacilin, concentrate for the preparation of a solution for local and external use in comparison with the drug Furacilin, tablets for the preparation of the solution, was carried out.

Objectives of the study: To determine the abnormal toxicity and locally irritating effect of the drug Furacilin in the Draize test (OECD No. 405).

Methods: Abnormal toxicity was performed according to the requirements of the State Pharmacopoeia of the Russian Federation (OFS.1.2.4.0004.15). The studied drugs were administered intraperitoneal volume of 0.5 ml (dose 25 mg/kg) at a rate of 0.1 ml per second. The Draize test was performed by instillation into the conjunctival sac of rabbit medicals at a concentration of 0.02% with a volume of 0.1 ml.

Results: After a single intraperitoneal administration of the studied drugs at a dose of 25 mg/kg, within 48 hours from the moment of their introduction, the death of animals was not observed in any of the experimental groups.

After instillation of 0.02% solutions of 0.1 ml of the studied drugs to rabbits, and subsequent observation after 1, 24, 48 and 72 hours of changes in the conjunctiva, cornea and iris, chemosis was not registered. The number of points in all parameters, in all experimental groups, did not exceed 0 points.

Conclusion: The obtained data indicate that Furacilin, a concentrate for the preparation of a solution for local and external use 4 mg/ml in its parameters of Toxicological safety and the absence of local irritant action at the site of application, comparable to the drug comparison Furacilin, tablets for the preparation of a solution for local and external use 20 mg.

Keywords: Nitrofural, Furacilin Tablets, Furacilin Concentrate for the Preparation of a Solution for Local and External Use, Abnormal Toxicity.

Introduction

Nitrofural (Furacilin) belongs to the group of nitrofurans. It has antimicrobial action. It is used as a liquid for washing and cleansing wounds, due to its antiseptic properties it slows down or stops the growth of microbial flora and the growth of fungi [7, 8, 15, 27, 28].The mechanism of action of nitrofurans is not fully studied. Nitrofurans are prodrugs that are activated by specific enzymes. Antibacterial activity of nitrofurans is derived from reductive metabolism of the nitro group catalyzed by nitroreductase-Zoi [12, 21, 25, 24, 29, 30]. Nitrofurans can be transformed by releasing nitric oxide to form toxic peroxynitrite and other oxidized derivatives [14, 26, 31]. Taking into account the formation of nitric oxide from nitrofurans, as well as existing antibacterial nitric oxide donors, there is an assumption that the antibacterial effect of nitrofurans may be due to the activity of nitric oxide [12, 6, 32, 33].We studied the effects of nitrofuran (nitrofural), of furacilin, nitrofurantoin, nifuroxazide and donors of nitric oxide - sodium nitro-prusside and isosorbide Mononitrate on the formation of biofilms of Pseudomonas aeruginosa PAO1 and Burkholderia cenocepacia 370. All compounds have been shown to increase the ability of these pathogenic bacteria to form biofilms at concentrations that do not inhibit bacterial growth in experimental conditions [22].

Antimicrobial activity of nitrofurans in vitro in relation to some pathogens correlates with the activity of drugs in vivo on experimental models. The activity of nitrofurans (nitrofurantoin, nitrofurazone, furazolidone, furaltadone, etc.) is shown in experiments on mice in infections caused by enterobacteria, vibrions, staphy-lococci and streptococci; in experiments on chickens and turkeys in infections caused by Salmonella, staphylococci, coccidia. In experiments on mice with infection

caused by pneumococcus, the drugs were not active [11, 34].

The mechanism of nitrofurans action on the microbial cell consists of several factors. The drugs are oxygen acceptors and disrupt the process of cellular respiration; nitrofurans inhibit the activity of a number of respiratory enzymes of the cell (pyruvate oxidase, glutathione reductase, aldehyde dehydrogenase). The drugs are eposed intracellular transformation: the process of restoring the nitrogroup under the action of bacterial flavoproteins. As a result, metabolites of nitrofurans are formed, which have a cytotoxic effect. Cytotoxic action of nitrofurans in combination with violation of cellular respiration causes the activity of some drugs (furazolidone, nifuratel) in high concentrations not only in the presence of bacteria and protozoa (Trichomonas, Giardia, dysentery amoeba), but also in respect of fungi, including the genus Candida. The drugs inhibit the biosynthesis of microbial DNA and extent RNA less. The mechanism of action of nitrofurans can not be considered fully deciphered, but it is specific only for drugs in this group. That is why nitrofurans are active against most strains of bacteria resistant to antimicrobial agents of other chemical classes [2, 12].

Furacilin affects various gram-positive and gram-negative bacteria: staphylococci (Staphylococcus spp.), Streptococcus (Streptococcus spp.), dysentery and E. coli (Shigella dysen-teria spp., Shigella flexneri spp., Shigella boydii spp., Shigella sonnei spp., Escherichia coli), Salmonella (Salmonella spp), pathogens of paratyphoid and gas gangrene (Clostridium perfringens), Giardia, Trichomonas, large viruses, etc.

It is effective at resistance of microorganisms to other antimicrobial agents (not from the group of nitrofuran derivatives). It inhibits the vital activity of fungal flora. The mechanism of action is based on the restoration of 5-nitrogroup microbial flavoproteins to form reactive amino derivatives that can cause changes in proteins (including ribosomal) and other macromolecules, leading to the death of cells of pathological microorganisms. Due to the fact that drug resistance develops slowly and does not reach a high degree, nitrofural is of particular importance in medical practice [1].

Despite the rapid development of experimental pharmacology [9, 16], the spread of recombinant drugs [23], drug design methods, which allow to create a highly selective drugs [17, 19], classical drugs [18, 10, 4, 11], including the nitrofuran derivate - furacilin, remain highly important.

The research of safety and pharmacological activity of the new drugs [2, 3, 5, 12, 13, 20, 18] plays a special role in providing the pharmaceutical market with new quality products.

To register the drug Furacilin, concentrate for the preparation of a solution for local and external use 4 mg/ml, which is a generic drug for the time-decided to use in the Russian drug Furacilin, tablets for the preparation of a solution for local and external use 20 mg, containing in its composition the active substance-nitrofural.

Objectives of the Study

The research of abnormal toxicity and local irritant effect in the Draize test (OECD No. 405) of the drug Furacilin, concentrate for preparation of solution for local and external use 4 mg/ml in comparison with the drug Furacilin tablets for preparation of solution for local and external use 20 mg.

Materials and Methods

Experiments were conducted on white laboratory mice and chinchilla rabbits. For the study were taken animals without external signs of the disease, which had a quarantine. Ethical principles of treatment of laboratory animals were observed in accordance with the "European Convention for the protection of vertebrates used for experimental and other scientific purposes. CETS No. 123".

The experiment on the study of abnormal toxicity included the following groups: the first – Furacilin, concentrate for the preparation of a solution for local and external use 4 mg/ml (n=10); the second – Furacilin (artificially aged), concentrate for the preparation of a solution for local and external use 4 mg/ml (n=10); the third – Furacilin, concentrate for preparation of solution for local and external application of 20 mg/ml (n=10); the fourth – Furacilin (artificially aged), concentrate for preparation of solution for local and external application of 20 mg/ml (n=10); the fifth– Furacilin, tablets for preparation of solution for local and external application of 20 mg (n=10).

The experiment for the Draize test included the following groups: the first – Furacilin, concentrate for the preparation of a solution for local and external use 4 mg/ml (n=10); the second – Furacilin, concentrate for the preparation of a solution for local and external use 20 mg/ml (n=10); the third – Furacilin, tablets for preparation of a solution for local and external application of 20 mg (n=10).

The research of the abnormal toxicity was performed according to the requirements of the State Pharmacopoeia of the Russian Federation (FFS.1.2.4.0004.15). The studied drugs were administered intraperitoneal volume of 0.5 ml (dose 25 mg/kg) at a rate of 0.1 ml per second.

The preparation of doses was carried out the following way: Furacilin, concentrate for the

preparation of a solution for local and external use 4 mg/ml: 0.125 ml of the concentrate solution was adjusted to 0.5 ml with water for injection; Furacilin, concentrate for preparation of solution for local and external use 20 mg/ml: 0,025 ml of the concentrate was adjusted to 0.5 ml with water for injection; Furacilin tablets for preparation of solution for local and external use 1 tablet (20 mg), was dissolved in 20 ml of water for injection.

Monitoring of animals was carried out within 48 hours from the date of administration of drugs. The drugs were considered to have passed the test if none of the experimental animals died within the prescribed period of observation.

When studying the locally irritating effect on the conjunctiva of the rabbit's eye, the studied drugs and the comparison drug were instilled into the conjunctival sac at a concentration of 0.02% with a volume of 0.1 ml.

Experiments began with 1 animal in each group, then the experiments continued on 2 animals in each group.

After the instillation of the studied drugs, the eye condition was assessed 1, 24, 48 and 72 hours after the use of the tested drugs.

Guidelines (conjunctiva, cornea and iris) the Guidelines presented in the OECD guidelines for the testing of chemicals test No. 405: acute eye irritation/corrosion.

Results

Studies have shown that after a single intraperitoneal administration of the studied drugs at a dose of 25 mg/kg, within 48 hours from their introduction, the death of animals was not observed in any of the experimental groups.

The studies showed that after instillation of 0.02% solutions of the studied preparations with a volume of 0.1 ml to rabbits, and subsequent observation after 1, 24, 48 and 72 hours of changes in the conjunctiva, cornea and iris, chemosis was not registered. The number of points in all parameters in all experimental groups did not exceed 0 points (table 1, Annex 2). The state of the controled eyes in all experimental groups was unchanged and corresponded to the state of intact eyes.

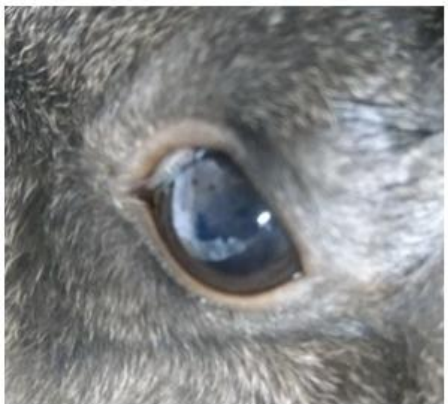

Figure-1: Controled eye of the rabbit, after instillation of Furacilin, concentrate for preparation of solution for local and external use 4 mg/ml, 72 hours after the instillation

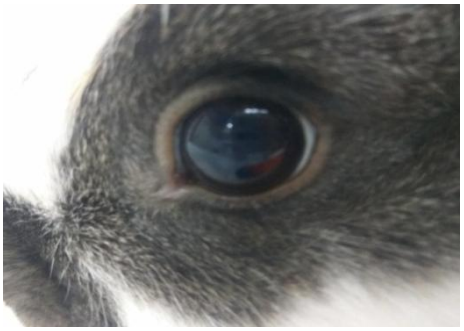

Figure-2: Controlled eye of the rabbit after instillation of Furacilin, concentrate for preparation of solution for local and external use 20 mg/ml, 72 hours after the instillation

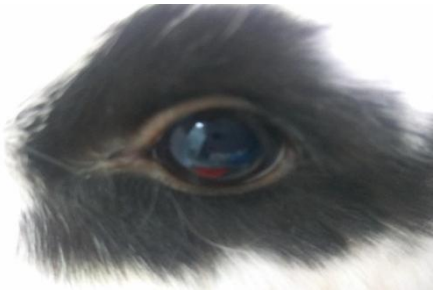

Figure-3: The controlled eyes of rabbits after instillation Furacilin tablets for preparation of solution for local and external use 20 mg, through 72 hours after the instillation

On the basis of the study, it was concluded that the drugs: Furacilin, concentrate for the preparation of a solution for local and external use 4 mg/ml, Furacilin, concentrate for the preparation of a solution for local and external use 20 mg/ml in a concentration of 0.02% do not have a locally irritating effect.

Thus, drugs Furacilin, concentrate for preparation of solution for local and external use 4 mg/ml (part 1), Furacilin, concentrate for preparation of solution for local and external use 20 mg/ml and Furacilin tablets for preparation of solution for local and external use 20 mg according to the study, possess good tolerability and do not have a local irritating effect.

Discussion

Investigation of abnormal toxicity of drugs Furacilin, concentrate for preparation of a solution for local and external use 4 mg/ml, Furacilin (artificially aged), concentrate for preparation of a solution for local and external use 4 mg/ml, Furacilin, concentrate for preparation of a solution for local and external use 20 mg/ml, Furacilin (artificially Aged), concentrate for the preparation of a solution for local and external use 20 mg/ml and a comparison drug Furacilin, tablets for the preparation of a solution for local and external use 20 mg, was carried out on males and females of white laboratory mice. The drugs were administered in a volume of 0.5 ml (dose 25 mg/kg) intraperitoneally at a rate of 0.1 ml per second. The subsequent observation period was 48 h. It was established that the investigated drugs and the reference drug in the dose of 25 mg/kg did not cause death of animals.

The study of the local irritant effect of Furacilin, a concentrate for the preparation of a solution for local and external use 4 mg/ml, Furacilin, a concentrate for the preparation of a solution for local and external use 20 mg/ml, and a comparison drug Furacilin, tablets for the preparation of a solution for local and external use 20 mg, was conducted male rabbits. Preparations in the form of 0.02% solutions were installed in the conjunctival sac in a volume of 0.1 ml.

Observations and assessment of the eye condition were carried out 1, 24, 48 and 72 hours after the use of the tested drugs. It was found that the studied drugs and the comparison drug when instilled into the conjunctival sac in the form of 0.02% solutions in the amount of 0.1 ml do not cause chemosis, damage or changes in the conjunctiva, cornea and iris in 1, 24, 48 and 72 hours.

Conclusion

According to the results of the research, it was concluded that the studied drugs do not have a toxic effect during the test in abnormal toxicity and do not have a locally irritating drift in the Draize test (OECD guidelines for testing chemicals test No. 405: acute irritation/corrosion)

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