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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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EFFECT OF SOME IMMUNOMODULATORY DRUGS ON EMBRYONIC DEVELOPMENT OF DANIO RERIO FISH

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Abstract.

At the current stage of healthcare development, the inclusion of immunomodulators in the complex pharmacotherapy of various immunoinflammatory and viral diseases is widely discussed, but due to the lack of sufficient research and a broad evidence base, not all drugs with similar properties are used in medicine. According to the information obtained from the instructions for the use of immunomodulators, it was obtained that the main contraindications to their use include the prescription of children, pregnant women, and women during breastfeeding. In this study, we evaluated the effects of immunomodulatory drugs: aminodihydrophthalazindione sodium and meglumine acridonacetate, on the early developmental stages of Danio rerio (Zebrafish) embryos.

Key words. Danio rerio, immunomodulatory drugs, pregnancy.

Introduction.

At the current stage of healthcare development, the inclusion of immunomodulators in the complex pharmacotherapy of various immunoinflammatory and viral diseases is widely discussed, but due to the lack of sufficient research and a broad evidence base, not all drugs with similar properties are used in medicine [1].

Immunomodulators are biologically active substances that, depending on the initial state of the immune system, either enhance its function or suppress it [2]. Immunomodulators are usually prescribed as an adjunct to existing therapy. This group of drugs has appeared relatively recently. According to the information obtained from the instructions for the use of immunomodulators, it was obtained that the main contraindications to their use include the prescription of children, pregnant women, and women during breastfeeding. At the same time, great attention is paid to hypersensitivity in an individual to the components of the drug [3].

When reviewing scientific studies, it can be seen that the list of authorized immunomodulatory drugs during pregnancy is limited and consists of several drugs that are prescribed with caution if necessary. Physicians are wary of using immunomodulators due to the lack of information on the safety of their use during the periods described above [4].

It is difficult to gather an evidence base for the use of immunomodulators during pregnancy. The difficulty manifests itself in the inability to draw conclusions, since the prescription of these drugs is carried out mainly in several states:

- women during complex therapy of tumor diseases, when later on the woman cannot get pregnant due to the consequences of the therapy performed or due to age.
- women during complex therapy of viral diseases, when fetal death may be observed, but no one usually identifies the cause [5].

The danger of many immunomodulatory drugs is that they are prescribed over the counter - this creates a significant problem, especially in the case of pregnant women, because many patients self-medicate various diseases and only as a last resort turn to doctors, often when it is already difficult to find the correct therapy [6].

The lack of evidence base, the seriousness of contraindications to the use of immunomodulators served as a basis for writing a research paper. Of the many experimental animals that are currently used for preclinical studies, small aquarium fish Danio rerio (Zebrafish) were chosen [7]. These fish have been gaining popularity in recent years and are rightly considered unique experimental models. Danio rerio (Zebrafish) fish have a high throughput capacity, transparent embryos, a genome 70% identical to the human genome, and a rapid development cycle, which allows us to study the development of organ systems during embryogenesis [8]. In 3 days, fish go through a developmental cycle from egg to larva. The fertilization process of Danio rerio (Zebrafish) fish is external (not in the body of the female), which makes it more accessible and convenient for research [9].

The applications of Danio rerio (Zebrafish) are multifaceted. Fish are used in the study of cancer, depressive disorders, drug intoxication and many others [10].

Based on a number of features, such a model is used to study embryotoxicity of drugs, which further allows us to draw conclusions about teratogenic effects on the body. Studies involving Danio rerio (Zebrafish) fish do not require significant time and money expenditures, which contributes to faster achievement of the goal, which is why they are often used in research and development [8-10].

The aim of the study was to evaluate the effect of immunomodulatory drugs: aminodihydrophthalazindione sodium and meglumine acridonacetate – on the early stages of development of Danio rerio (Zebrafish) embryos.

Objectives of the study:

1. to evaluate the effect of immunomodulators on the embryonic development process of Danio rerio (Zebrafish) fishes.
2. to confirm or refute the main contraindication to the use of immunomodulators, namely the impossibility of their use in pregnancy.
3. to evaluate histologic changes of Danio rerio fish embryos from different experimental groups at the stages of 24; 48; 72 hours from the moment of spawning.

4. to carry out a comparative analysis of two drugs with immunomodulatory activity on the behavior of Danio rerio fish - aminodihydrophthalazindione sodium and meglumine acridonacetate.

Materials and Methods.

The study was carried out in the laboratory of the Department of Pharmacology and Pharmacy named after academician S.V. Anichkov. The object of the study were adult fish Danio rerio (Zebrafish) of natural color (n=90), which were specially bred for scientific-research work. The fish were placed in 30 L aquariums with full equipment, where the conditions necessary for their habitat were constantly maintained: temperature regime (25-26°C), light regime, air aeration conditions, water pH and nitrate level. The nitrate level was important because the aquariums, despite being fully equipped, did not contain any natural plants, but only artificial ones.

The following groups were formed (Figure 1):

- control group (n=30).
- experimental group №1 (n=30) - aminodihydrophthalazindione sodium.
- experimental group №2 (n=30) - meglumine acridonacetate.

From a large number of immunomodulatory drugs, two drugs were chosen for the study, which are often prescribed by physicians but do not have a broad evidence base:

- aminodihydrophthalazindione sodium is an immunomodulatory drug with anti-inflammatory effects.
- meglumine acridonacetate - immunomodulatory, antiviral drug.

In order to achieve maximum bioavailability of drugs in the body of fish, the following dosage forms of drugs were chosen:

- aminodihydrophthalazindione sodium - powder for solution preparation in vials.
- meglumine acridonacetate - solution in ampoules.

Danio rerio (Zebrafish) fish received the drugs mainly through the gills. For each experimental group a certain dose of the drug was selected: experimental group №1 (aminodihydrophthalazindione sodium) - 20 mg, experimental group №2 (meglumine acridonacetate) - 50 mg. For the full effect of the drug on the body of fish, it was diluted in a 5-liter tank of water, where the fish were placed for 30 minutes, every other day, for 10 days in accordance with the dosage. After completion of the course of drug administration, the fish were placed in special tanks to obtain embryos.

Results.

During 10 days the fish received aminodihydrophthalazindione sodium and meglumine acridonacetate according to the selected dosage. At the first administration of the preparations intoxication was noticed, manifested by redness in the area of gill arches, which was especially pronounced in experimental group №2. On the other days intoxication as well as toxic effects were not observed.

The behavior of the fish after application of the drugs was evaluated in comparison with the control group. In experimental group №1 fish moved throughout the aquarium, quickly moving from the lower to the upper level of swimming. In the experimental group №2 on the first day of application of drugs revealed a slight decrease in the activity of swimming fish in the aquarium. After the application of drugs in Danio rerio (Zebrafish) fish increased the reaction to food and the approach of any object (hand, phone, light) to the aquarium in both experimental groups.

The longest in terms of time was the second stage of the study, which amounted to 21 days (Danio rerio breeding stage in order to obtain embryos).

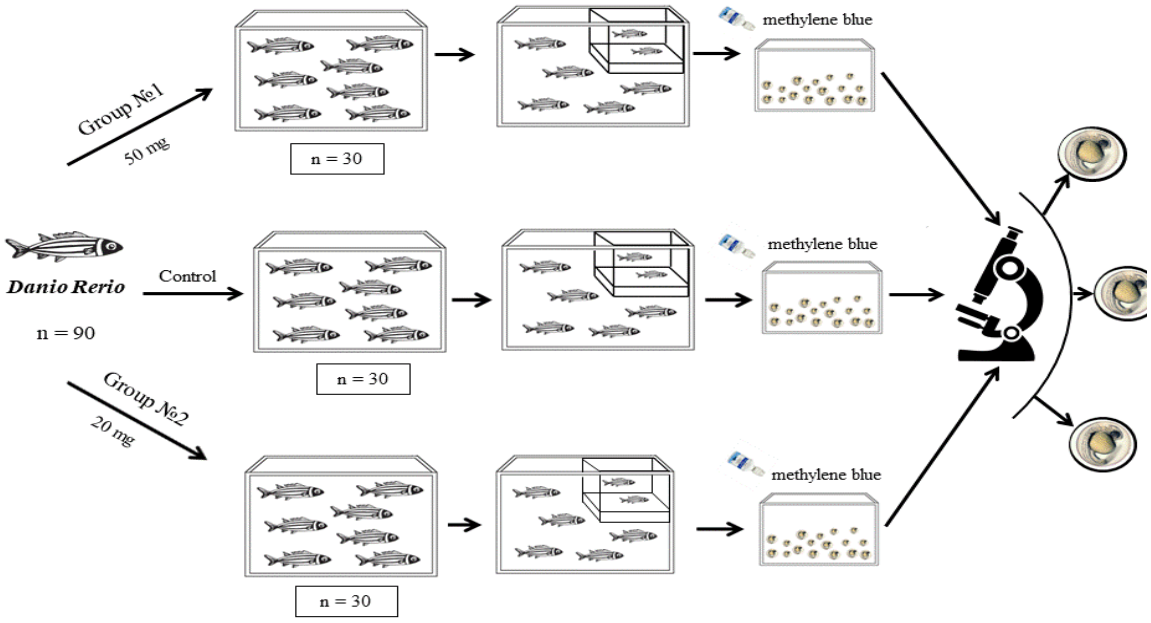


Figure 1. *Research design.*

The study included the following stages:

Stage 1: *administration of drugs to Danio rerio (Zebrafish) fish and observation of their response and behavior.*

Stage 2: *breeding Danio rerio fish to obtain embryos.*

Stage 3: *microscopy of the obtained embryos.*

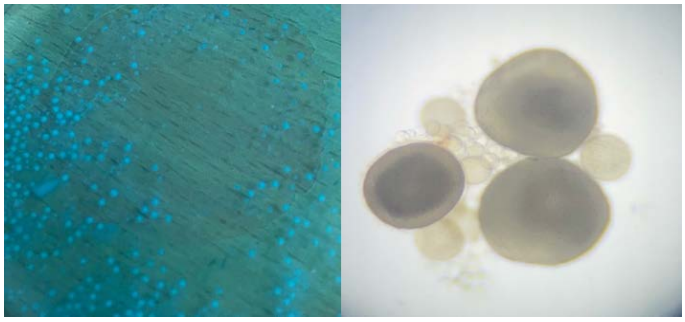


Figure 2. *Eggs of Danio rerio fish of the control group after spawning.*

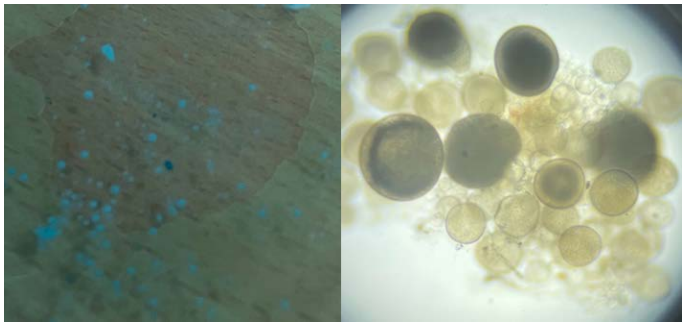


Figure 3. *Eggs of Danio rerio fish of experimental group №1 (aminodihydrophthalazindione sodium) after spawning.*

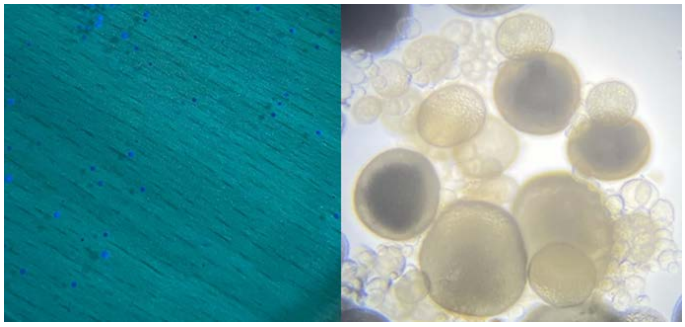
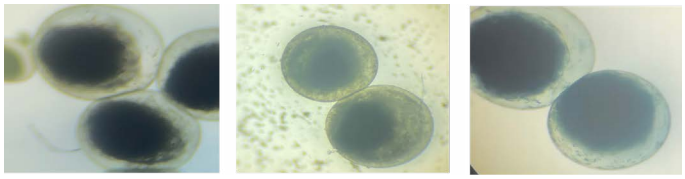
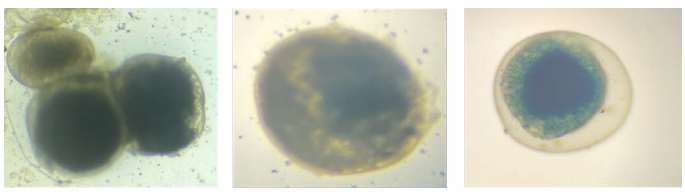


Figure 4. *Eggs of Danio rerio fish of experimental group №2 (meglumine acridonacetate) after spawning.*



Control Group №1 Group №2

Figure 5. *Danio rerio fish eggs 24 hours after spawning.*



Control Group №1 Group №2

Figure 6. *Danio rerio fish eggs 48 hours after spawning.*

After the end of exposure of Danio rerio (Zebrafish) fish to immunomodulatory drugs, separation into females and males was performed. When separating into sexes, attention was paid to coloration (males are brighter than females), size (females have a rounded abdomen, elongated body shape). The fish were then placed in specialized tanks where the spawning process of eggs took place. In each tank, 4 females and 8 males were transplanted in all studied groups. Feeding was carried out not only in the morning but also in the evening. On day 8, rounding of the abdomen of the fish in the tanks was noticed, indicating the imminent emergence of eggs. After 7 days, the males were moved to a common aquarium.

After 20 days of research, no eggs were obtained, considering that by all indicators Danio rerio fish were ready to spawn in all groups, only in the control group we observed a few eggs. Based on this, after analyzing the literature, eggs were obtained unnaturally by pressing on the abdomen of the female, with most of the females alive.

On day 21 of the study, eggs of Danio rerio (Zebrafish) were obtained and placed in three petri dishes, with the highest number of eggs observed in the control group, and the group that received meglumine acridonacetate had the least number of eggs. Methylene blue was added to each of the cups by pipette in the amount of three drops per cup. This was done to reduce the risk of fungal infection of eggs. It was observed that in the group receiving meglumine acridonacetate the eggs inside were completely coloured blue, while in the other groups no such phenomenon was observed. It is assumed that such an outcome of staining was influenced by the composition of meglumine acridonacetate namely acridonacetic acid, which gives the drug a yellow colour.

The microscopy stage was performed on an optical microscope, at a magnification of 40X.

When conducting microscopy of eggs immediately after spawning, the usual shape of eggs (rounded shape with darkening inside) was observed in all groups under study, the development of organ systems did not occur, because in Danio rerio fish the development cycle lasts about 3 days and only 24 hours after spawning the beginning of organ formation is noticeable.

Microscopy of eggs 24 hours later showed minor differences from the picture obtained immediately after spawning. The initial stage of organ laying was not observed.

On the 2nd day (48 hours after spawning) no special changes were found, but clear boundaries and pronounced blue-green colour were seen in group №2 compared to other groups.

Seventy-two hours after spawning no fry development occurred, the same microscopic picture was observed as on the first day, which allowed us to conclude that the drugs could provoke a disruption of the process of embryonic development. In the control group, which did not receive drugs, also no fry was obtained, but on the third day a change in the shape of the egg and the beginning of the formation of the head and tail of the fish was observed.

Conclusion.

It was revealed that the immunomodulators under study provoked disruption of the reproduction process of Danio rerio

(Zebrafish), as in normal course eggs appear on the 10th day after enlargement of the fish's abdomen, and in this study, eggs were obtained on the 21st day, and by unnatural means, which indicates a negative effect on the organism of the pregnant female.

One of the main contraindications to the use of both drugs: aminodihydrophthalazindione sodium and meglumine acridonacetate - has been confirmed. The drugs should not be administered during pregnancy.

Microscopy of the obtained embryos evaluated changes 24; 48; 72 hours after spawning and revealed a delayed process of embryonic development. One of the main features of Danio rerio fish includes a rapid development cycle, which lasts 3 days, and on day 3 (72 hours) the same developmental stage was observed as on day 1 (24 hours).

A comparative analysis of aminodihydrophthalazindione sodium and meglumine acridonacetate on the behavioral activity of Danio rerio fish was carried out, in which a slight change in the behavior of Danio rerio fish in the group with meglumine acridonacetate was observed, manifested in longer and irregular swimming.

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